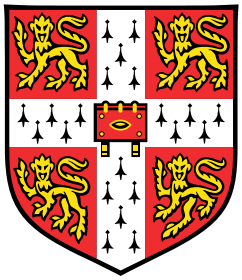
Using mathematical models to evaluate and inform immunisation strategies with MenAfriVac in the African meningitis belt



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This dissertation is submitted for the degree of
Doctor of Philosophy

Darwin College

April 2019

I would like to dedicate this thesis to my loving parents ...

Σας αγαπω πολυ

Declaration

- This dissertation is the result of my own work and includes nothing which is the outcome of work done in collaboration except as declared in the Preface and specified in the text.
- It is not substantially the same as any that I have submitted, or, is being concurrently submitted for a degree or diploma or other qualification at the University of Cambridge or any other University or similar institution except as declared in the Preface and specified in the text. I further state that no substantial part of my dissertation has already been submitted, or, is being concurrently submitted for any such degree, diploma or other qualification at the University of Cambridge or any other University or similar institution except as declared in the Preface and specified in the text.
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Andromachi Karachaliou Prasinou
April 2019

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The countries of the African meningitis belt suffer from frequent epidemics due to meningococcal meningitis. The introduction of a tailor-made vaccine, known as MenAfriVac, in these countries through mass campaigns of 1-29 year olds has led to a remarkable decline in the burden of disease due to *Neisseria meningitidis* serogroup A. The aim of this work is to identify immunisation strategies with MenAfriVac that best sustain population protection in the long-term and predict vaccine impact across all 26 meningitis belt countries.

Firstly, I developed an age-structured transmission dynamic model to explore the impact of a range of different immunisation schedules. Numerical simulations of the model show a period of very low incidence following MenAfriVac introduction, while strong resurgence is predicted in the absence of any long-term immunisation strategy. Of the strategies considered, the introduction of the vaccine into the Expanded Programme on Immunisation at 9 months, 5 years after the initial campaign, together with a mini catch-up campaign resulted in the lowest average annual incidence.

Next, my model is compared to an existing model, published two years earlier through a model comparison exercise. The comparison exercise identified a number of errors in the other study which explained the different predictions made by the two models and also led to a correction to the original study being published by the authors.

As part of the Vaccine Impact Modelling Consortium, the model was adapted and used to provide estimates on the impact of MenAfriVac on disease incidence for the 26 countries of the meningitis belt under the current schedule of each country. The model consists of 100 age groups and keeps track of the number of cases, deaths and Disability Adjusted Life Years (DALYs) for each age group per year for the period 2010-2100. Assuming that the current schedule continues unchanged until 2100, the model predicts that more than 9 million cases will be prevented in total across all 26 countries.

Further, the routine immunisation of school-age children is simulated as an alternative strategy to better understand the role of vaccine induced protection, as new data suggest that antibody response is short-lived when children under the age of two years are vaccinated. Assuming that vaccine protection lasts longer for individuals targeted after

the age of five years, model simulations suggest that vaccination of older children would be more efficient in reducing the disease incidence and would also result in a smaller number of people needed to vaccinate to prevent one case.

The main conclusion of this work is that sustained use of MenAfriVac is essential to maintain high levels of direct and indirect population protection. Results from this thesis have been used to inform the current immunisation strategy in the countries of the African meningitis belt. Assuming that vaccine duration is shorter for children less than 5 years old, it may be wiser to change the age of routine immunisation and target older children instead. This conclusion can be useful in the near future to inform strategies which will include the new pentavalent vaccine.

Acknowledgements

- A very big thank you to my supervisor, Caroline Trotter, for her support, guidance and encouragement. She has been a constant source of motivation and inspiration to me and without her on-going invaluably constructive criticism this PhD would not have been achievable.
- I would also like to thank my co-supervisor, Andrew Conlan, for his valuable guidance at various stages of my research.
- I thank all the members of the DDU, past and present, and especially, Laura Cooper, David Price and Katy Gaythorpe for all stimulating discussions and insightful comments.
- To my friends, thank you for offering advice and for supporting me through this process.
- I must thank my family for inspiring me to follow my dreams. I am grateful to my big sister Anastasia for always being there for me. Thank you and Guillaume for making me a proud auntie (twice) and nona. My special thanks are for my parents, Christos and Alexandra, for their continuous love and support, both emotional and financial. Thank you for believing in me.
- The best outcome from these past four years is meeting and marrying the best person out there for me. My great appreciation goes to my husband, Agis, who has been a constant source of support and encouragement.

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Chapter 1

Introduction

1.1 Context

Neisseria meningitidis, the meningococcus, is an important cause of bacterial meningitis [2]. Meningococcal meningitis is fatal in around 10% of cases and can cause severe brain damage in survivors [3]. The epidemiology of meningococcal meningitis varies greatly throughout the world, but an area of sub-Saharan Africa, known as the meningitis belt, has by far the highest incidence of disease [4].

A new meningococcal group A conjugate vaccine, commonly known as MenAfriVac, developed specifically for Africa [5, 6], was first introduced in 2010 through mass immunisation campaigns targeting individuals between 1 and 29 years old [7], with the aim of eliminating epidemic meningitis as a public health problem.

Before 2010, repeated epidemics have been reported in the African meningitis belt with weekly incidence reaching up to 100 cases per 100,000 population [8]. Group A meningococcus accounted for an estimated 80% of all cases of meningitis [9]. Since the introduction of MenAfriVac, the proportion of serogroup A cases has declined remarkably [10–12].

The aim of this thesis is to develop and apply mathematical models to investigate the epidemiology of meningococcal carriage and disease and predict the impact of further vaccination with MenAfriVac.

1.2 Outline of the thesis

This thesis is organised as follows:

- **Chapter 2** provides a description of the epidemiology of meningococcal meningitis around the world and more specifically in the African meningitis belt before and after the introduction of MenAfriVac, followed by a discussion on the usefulness of mathematical models in guiding public health action and the models related to meningococcal meningitis that are developed up to now.

- **Chapter 3** presents the development of a meningitis transmission dynamic model. The model is then applied to investigate the impact of various immunisation strategies with MenAfriVac in Burkina Faso. The strategies are compared to a scenario in which there is no long-term immunisation schedule.

- **Chapter 4** presents a comparison of my model with a previously published model, triggered by observed differences in their results.

- **Chapter 5** presents the work undertaken as part of the Vaccine Impact Modelling Consortium (VIMC). The model presented in Chapter 3 is adapted to meet the requirements set by VIMC and is used to provide estimates on disease burden in the 26 countries of the African meningitis belt.

- **Chapter 6** presents my work on simulating alternative vaccination strategies targeting school-aged children instead of infants for routine immunisation. Key assumptions about the duration of vaccine-induced immunity are revisited based on newly available data. The model from Chapter 5 is used to provide estimates on disease burden in Chad under a range of different assumptions regarding the duration of protection. The potential impact of an additional mass immunisation campaign using the novel pentavalent vaccine on *Neisseria meningitidis* serogroup A is also explored.

- **Chapter 7** concludes this thesis with a discussion on the implications of my findings on vaccine policy. The key limitations and weaknesses are summarised, followed by a discussion on areas of future work.

The definition of the age range when I refer to the terms infants, children, adolescents and young adults throughout this thesis is given below.

Term	Age range
Infants	<1 years
Children	1-9 years
Adolescents	10-19 years
Young adults	20-29 years

1.3 Publications

- The work in Chapter 3 has been published as the following paper (attached at the end of this thesis in Appendix B):

  A. Karachaliou, A. J. K. Conlan, M-P. Préziosi, and C. L. Trotter. Modeling long-term vaccination strategies with MenAfriVac in the African meningitis belt. Clinical Infectious Diseases, 61(Suppl 5):S594–600, Nov 2015.

  I was the lead author of this paper and I developed the code and analysed all the results. I also wrote the first draft of the manuscript. Dr Andrew Conlan contributed to this paper by providing technical advice and guidance. Dr Marie-Pierre Preziosi provided consultation and data on vaccine coverage. Dr Caroline Trotter was the principal investigator.

- I used the model from Chapter 3 to produce estimates for a cost-of-illness study published (attached at the end of this thesis in Appendix B) as follows:

  A. Colombini, C. L. Trotter, Y. Madrid, **A. Karachaliou**, and M-P. Préziosi. Costs of *Neisseria meningitidis* group A disease and economic impact of vaccination in Burkina Faso. Clinical Infectious Diseases, 61(Suppl 5):S473–482, Nov 2015.

Chapter 2

Background

2.1 *Neisseria meningitidis*

Meningitis is a severe infection of the meninges, the membranes surrounding the brain [2]. Meningococcal meningitis is a bacterial form of meningitis, caused by the bacteria *Neisseria meningitidis*, also referred to as meningococcus. *N. meningitidis*, first recognised in 1805, only affects humans and is a major cause of bacterial meningitis worldwide. While recognised as an important cause of disease, the typical habitat of meningococcus is the human nasopharynx and acquisition of the bacterium in most cases leads to a harmless colonisation [13].

Strains of *N. meningitidis* are classified into distinct serogroups on the basis of the chemical composition of their capsule. There are 12 serogroups, 6 of which, namely, A, B, C, W, X and Y, are the primary cause of disease in most parts of the world [14]. Some meningococci do not possess the genes encoding a capsule; these are known as capsule null (cnl). The capsule enhances the survival of the organism during the invasion of the bloodstream [15] while the absence of a capsule is believed to allow the bacterium to evade the human's immune response while in the carrier state [16]. Meningococci can also control the expression of the capsule through phase variation. Invasive disease is a rare outcome of colonisation by a capsule-deficient strain; the first reported fatal case of meningococcal disease caused by a cnl strain was in 2005 [17].

2.2 Epidemiology of carriage

The meningococcus is transmitted from human to human through the exchange of respiratory secretions during very close contact [13]. The reported prevalence of carriage

is in the range 1%-30% [18, 19] and varies greatly by age, sex and region [20]. Studies have shown that common risk factors associated with high prevalence of carriage are smoking, crowding in pubs or universities, intimate kissing and preceding viral infections [21–23]. In industrialised countries, a systematic review of carriage prevalence showed that carriage is rare in infants and young children, rises to a peak in late teen years and then gradually declines in older age groups [20]. As most studies are point prevalence studies rather than longitudinal, the duration of carriage is not very well defined in any setting. An episode of carriage may be transient or last for a few months before it is cleared [24, 25]. Different patterns of carriage have been described in the African meningitis belt [26], as described in more detail below.

2.3 Epidemiology of disease

Meningococcal disease incidence differs geographically. Many countries, including most high-income countries, suffer from endemic meningococcal disease with low incidence [4]. Most cases are sporadic, with occasional small clusters of epidemiologically linked cases occurring in higher education establishments. Occasionally, a country, or regions within a country, may experience 'hyperendemic periods' of elevated incidence of more than 10 cases per 100,000 population annually. New Zealand experienced such a 'hyperendemic period' between 1996 and 2003, with annual incidence consistently above 13 cases per 100,000 population [4]. Large-scale mobilisation of troops during World War II resulted in a large number of cases and deaths in the United States but outbreaks have been rare since [27, 28]. The annual pilgrimage in Mecca attracts a vast number of people from all over the world all year. In 1987, a virulent meningococcal outbreak was spread globally by a group of pilgrims returning to their home town [22].

In certain regions of the world, epidemics of disease occur periodically but irregularly. The scale of these epidemics is entirely different from hyper-endemic disease. The epidemic threshold defined by the World Health Organisation (WHO) is a weekly incidence of 10 cases per 100,000 (usually at a district level) and over the course of an epidemic season, cumulative incidence can be well in excess of 100 cases per 100,000 population. Most frequently recurring epidemics have been observed in the semi-arid area of sub-Saharan Africa with attack rates in the range of 100-800 cases per 100,000 population [4]. Repeated epidemics have also been reported in India and China over the last century, but China has lost the epidemic cyclic activity since the widespread use of meningococcal polysaccharide serogroup A vaccines in the 1970s [29].

For reasons not fully understood, the overall attack rates across developed countries have decreased substantially over the last decades. It is believed that population immunity to the strains currently circulating as well as changes in the prevalence of behavioural risk factors have contributed to the decline of the incidence [30]. In the United States and Europe, over the last 40 years, the estimated weekly incidence is around 1-3 cases per 100,000 population and small periodic outbreaks characterise the disease [4]. Why there are such different patterns of disease in different areas of the world and over time is not clear, certain differences in the predominant strains may be more important as are environmental factors and socioeconomic status.

Patterns of disease differ greatly to patterns of carriage. There is higher incidence observed in children under the age of five with a smaller secondary peak in teenagers [19]. Although meningococcal meningitis is primarily a disease of children and young adults, epidemic outbreaks, especially in sub-Saharan Africa, tend to involve adolescents and young adults. Disease outbreaks are also sensitive to seasonal effects. In most countries, infections occur in annual seasonal cycles.

2.4 African meningitis belt

Countries in sub-Saharan Africa suffer from frequent epidemics of meningococcal disease. The first proven outbreak of meningococcal meningitis in Africa was recorded at the beginning of the 20^{th} century in northern Nigeria and it is argued by Greenwood [8] that the meningococcus was brought to West Africa by pilgrims or followers of the Mahdi on their return home.

In 1963, Lapeyssonnie defined the meningitis belt, as the region in sub-Saharan Africa where the rates of incidence of meningitis are the highest worldwide. In his description, there was no clear definition of the belt's location nor were there any clear borders. The most recent definition of the belt came in 2002 by Molesworth *et al.* who used reports of meningitis epidemics from the last two decades of the 20^{th} century [31]. It is now generally accepted that the African meningitis belt spans all the way from Ethiopia to Senegal [8]. Twenty six countries lie, either entirely or partially, in the "expanded meningitis belt". The total population of these countries exceeds 750 million, while more than 400 million of these individuals are considered to be at high risk.

Recurrent epidemics of meningococcal disease have been reported throughout the African meningitis belt since the description of the disease [8]. Broutin *et al.* [32], using wavelet analysis, showed that the frequency of the epidemics in the countries of the

meningitis belt is every 8-12 years and that although huge epidemics may affect several countries at the same time, the epidemic cycle is not synchronised across countries. The weekly incidence rates during epidemics can reach up to 100 per 100,000 population in individual communities [8, 33]. According to WHO, the number and intensity of epidemics have been increasing since the late 1970s affecting the lives of hundreds of thousands of people [34]. The largest epidemic took place in 1996-1997, resulting in 250,000 cases and 25,000 deaths. The number of cases of suspected meningitis over time in Chad is shown in Figure 2.1, illustrating the variation in disease over time.

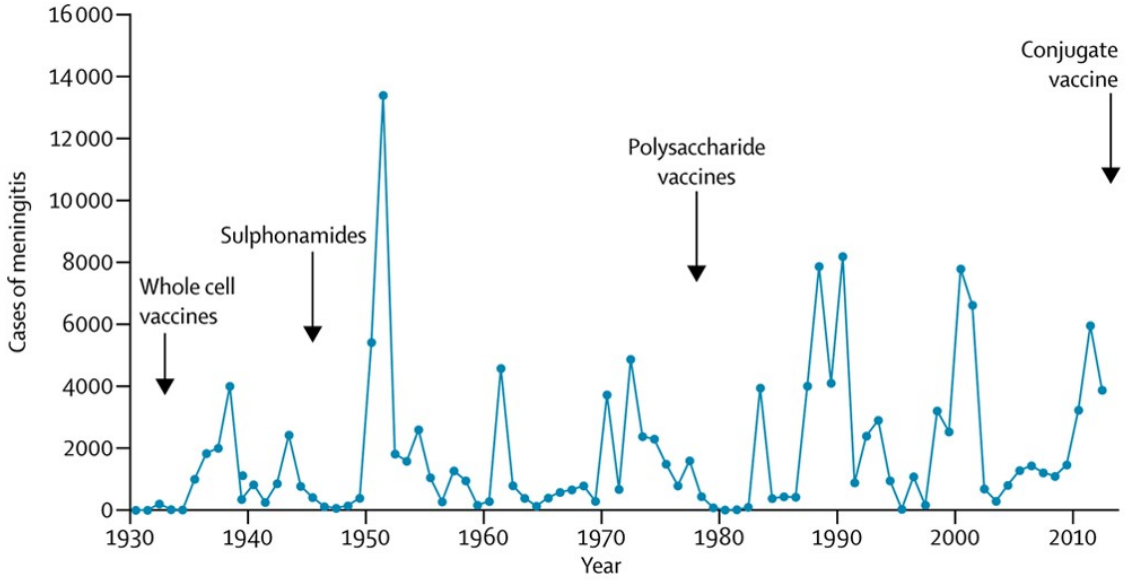

Fig. 2.1 Time series showing the number of suspected cases of meningitis in Chad 1940-2012. Figure: Daugla *et al.* [10].

Meningitis in Africa is highly seasonal. During the dry season between December to June, dust winds and cold nights lead to upper respiratory tract infections and result in an increased risk of meningococcal disease. The number of cases drops every year with the onset of the rains. There are recurrent multiannual epidemic waves on a large national scale. Large epidemics may span 2 or more dry seasons, with very few cases during the intermediate rainy seasons [8, 32, 33]. During non-epidemic years, even during the dry season, the number of cases is considerably lower than the number of cases during epidemic years. Over the last decade, several studies have been conducted trying to investigate the relationship between the climate and the incidence of meningitis [35–37]. All the studies conclude that dust may have a significant impact on the meningitis season. It is not clear, however, whether climatic variation affects the meningococcus directly.

One hypothesis trying to explain climate impact on disease incidence is an increase in the invasion rate (i.e. the rate at which carriers develop invasive disease) due to damage of the pharyngeal mucosa caused by high dust loads. Additionally, close contacts of individuals who take refuge from the strong winds in closed spaces can contribute to a higher transmission rate. Finally, the immune system can be vulnerable due to co-occurrence of viral respiratory infections, which can facilitate transmission and/or invasion of disease [38, 39].

In 2003, Molesworth *et al.* developed the first forecasting spatial model which predicts the probability of a future meningitis epidemic in areas of the African meningitis belt [40]. The model was used to derive a risk map of epidemic meningitis and they identified low humidity to be the most important factor associated with the occurrence of epidemics in sub-Saharan Africa.

2.4.1 Description of epidemiology of meningitis across the African meningitis belt

Seasonal attack rates can reach up to 800 cases per 100,000 at the district level [41]. *Neisseria meningitidis* serogroup A (NmA) is responsible for the majority of epidemics across the African belt [9, 42]. Lingani *et al.* [12] published a study recently reporting that there were more than 340,000 suspected and confirmed cases of meningitis due to NmA in ten countries of the African belt over ten years. There was a peak in the incidence rate of around 25 per 100,000 population in 2009 due to a large epidemic of NmA. The case fatality was around 10%, comparable to developed countries, while it was lowest during the epidemic year 2009. A study looking at the case-fatality ratio (CFR) of bacterial meningitis in the African meningitis belt has shown that CFR was lower for serogroup A (5.5%) than for other serogroups (12%) [43]. Therefore, the low case fatality reported in 2009 may reflect the high proportion of cases due to NmA (77%). Another explanation could be that reporting was weaker during the epidemic season. There appears to be no association between case fatality and age or sex [44].

Age distribution of cases varies between epidemic years and different countries but children 1-14 years of age account for around 75% of all cases while under five-year-olds account for 40% [18, 45]. Meningitis is rare amongst individuals aged more than 30 years. In 1999, Campagne *et al.* [46] conducted an extensive study looking at the epidemiology of meningitis in Niamey, Niger between 1981 and 1996. They reported a mean annual incidence of 101 cases per 100,000 population and they found a similar age distribution

between epidemic and non-epidemic years. This is probably still the best descriptive study of meningitis epidemiology in the belt.

Carriage prevalence can reach more than 10% of the population during an epidemic [47]. Contrary to the age distribution of meningitis cases, carriage prevalence is higher for individuals 5-30 years old than for infants. A number of carriers older than 30 years are also observed during epidemics. Meningococcal carriage in the African belt is not very well understood. A systematic review published in 2007 [18] showed that overall carriage prevalence of meningococci was in the range of 3.5%-35%. A large recent study in Burkina Faso [48] set a baseline carriage of NmA of 0.39%. The MenAfriCar consortium conducted 20 standardised surveys in seven countries across the African meningitis belt at approximately the same time [26]. Their findings confirm the results of previous studies undertaken at different sites, different times and with different techniques. They concluded that meningococcal carriage in the African belt is both complex and highly dynamic both in terms of prevalence of carriage and meningococcal genogroup.

The socioeconomic implications of epidemic meningitis are alarming. Most countries are struggling to respond appropriately to the needs of control and prevention of the disease. During the epidemic period 2006-2007 in Burkina Faso, the total national costs exceeded 9 million US$. That is, around 2% of the country's annual national health spending [49].

2.4.2 Immunisation

Until recently, the epidemics were controlled by mass vaccination with polysaccharide vaccines. Two epidemic thresholds are defined by WHO to guide the different actions needed depending on the phase of the epidemics. The alert threshold is set to be 3 cases per 100,000 individuals in districts where the total population is more than 30,000. When the alert threshold is passed, investigation is launched and the countries check their preparedness for an epidemic. In the case in which a neighbouring area is suffering from an epidemic, vaccination starts. When the epidemic threshold, 10 cases per 100,000 population, is passed, the emergence of an epidemic is confirmed, the people are informed and mass vaccination of targeted age groups begins. A single dose of the polysaccharide vaccine induces a rapid response of antibodies in more than 85% of individuals above the age of four years and protection lasts for at least one year. A modelling study published in 2014 showed that reactive campaigns with polysaccharide vaccine could reduce the number of cases by as much as 50% at a local level provided that they are conducted early [50]. Although a good antibody response is observed, the vaccine fails to reduce the

carriage prevalence amongst vaccinated individuals [51]. Response is poorer in infants and protection is short; hence, routine immunisation is not recommended. The costs associated with this strategy are enormous. During an epidemic year, the cost for the reactive vaccination campaigns can exceed 8 million US$ [49].

Meningitis Vaccine Project (MVP)

In May 2001, the Bill and Melinda Gates Foundation announced a global health grant in support of the collaboration between the World Health Organisation (WHO) and the Program for Appropriate Technology in Health (PATH) [52]. The Meningitis Vaccine Project (MVP) was a ten-year project with the elimination of NmA from the African meningitis belt as its ultimate goal. To achieve their goal, MVP was responsible for developing, licensing and introducing a tailor-made vaccine for use in Africa [53–55].

Existing effective conjugate vaccines can cost over $50 per dose. The meningitis belt is made up of some of the poorest countries in the world that cannot afford to pay more than one percent of that amount. Cost was the primary constraint to the introduction of a new conjugate vaccine. For that reason, a cheaper solution needed to be found. MVP partnered with the Serum Institute of India Ltd, who agreed to develop a vaccine at a target cost of $0.40 per dose [5, 6].

MenAfriVac

MVP developed a serogroup A meningococcal polysaccharide-tetanus toxoid protein conjugate vaccine (MenAfriVac or PsA-TT). The combination of meningitis bacteria polysaccharide capsule with a carrier protein is far more potent than the polysaccharide vaccines that were used previously.

Trials began in 2005 in India and Africa and the vaccine was found to be safe and highly immunogenic [56]. Besides being very effective, MenAfriVac has one more significant advantage. Most vaccines require to follow the so-called cold chain [57]. That is, they need to be stored cool from the point of storage all the way to delivery in the field. This is a considerable challenge in the heat of the African countries. MenAfriVac is licensed to be used in Controlled Temperature Chain (CTC) [58] and can last for up to four days without refrigeration. This provides enough time for people living in remote areas to reach the vaccination stations.

In December 2010, Burkina Faso was the first country to introduce MenAfriVac via a national mass immunisation campaign [7]. The campaign targeted individuals 1-29

years old, which is approximately 70% of the population of the country. More than 11 million individuals were given one dose of MenAfriVac in a period of 10 days. The mass campaign achieved very high coverage reaching more than 95%. Two more countries, Mali and Niger, initiated their mass immunisation campaigns in the year 2010. The campaigns were implemented in 2 phases and were completed in 2011. The vaccine is being rolled out across the 26 nations of the African meningitis belt over the course of several years (Figure 2.2). By 2020, MenAfriVac is expected to offer protection to the entire population of the African meningitis belt. The coverage is consistently high across all countries that have implemented the mass immunisation campaigns [59–62]

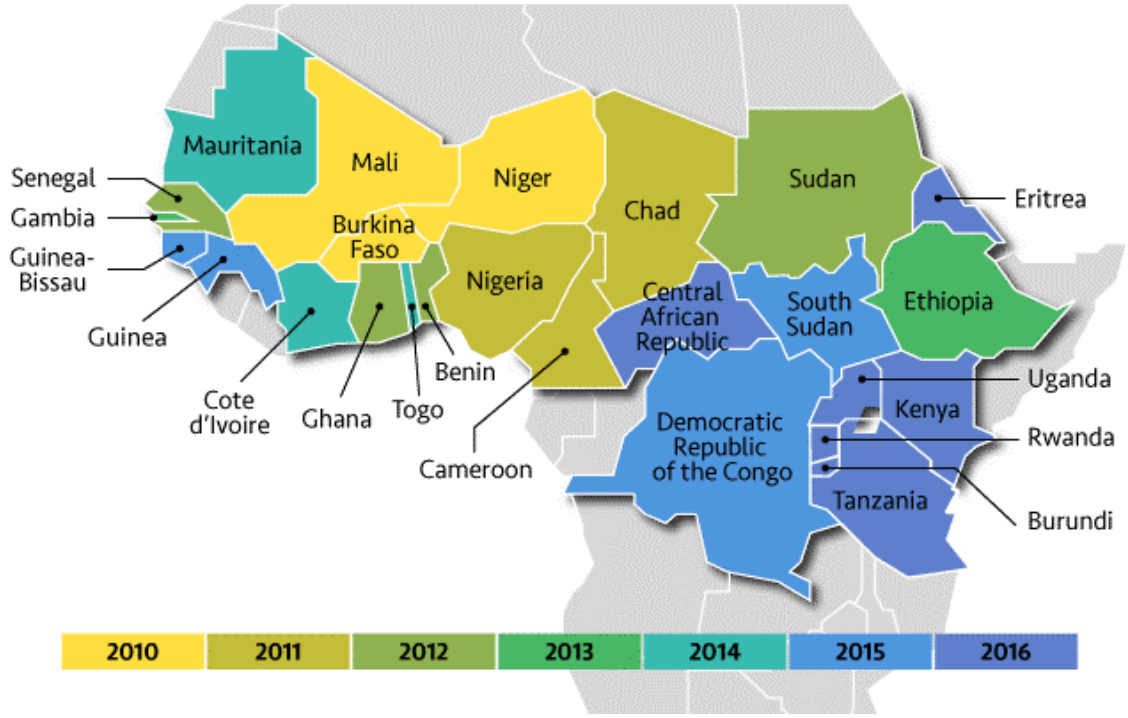

Fig. 2.2 The MenAfriVac is being rolled out across the 26 countries of the African meningitis belt. Image taken from www.path.org.

2.4.3 Impact of MenAfriVac

The initial mass immunisation in Chad was completed in two phases. The first phase, in which 20% of the 1-29 year olds received one vaccine dose, took place in 2011. The rest of the target population was vaccinated the following year, in 2012. More than 1.8 million people received the MenAfriVac in 10 days in 2011. There was a 94% difference in the incidence levels between vaccinated and non-vaccinated regions and despite enhanced

surveillance, no cases of NmA were reported in the vaccinated regions. Only 1 carrier was identified after vaccination in a rural area with a carriage prevalence of 0.75% (32/4278 individuals) two months before the campaigns took place [10]. There was a 98% decrease in the prevalence of NmA carriage in all age groups. Niger introduced MenAfriVac in 2010 and the disappearance of serogroup A meningococcus was noted in 2011 [11]. In addition to the dramatic decline of NmA cases, at the time of writing, prevalence of carriage remains at very low levels following MenAfriVac vaccination [26, 12, 63–66].

Apart from the great success of the vaccine in eliminating NmA, studies have shown that MenAfriVac has also boosted tetanus immunity and it is possible that it can have an impact on the incidence of neonatal tetanus in sub-Saharan Africa [67, 68].

Before mass immunisation, serogroup A predominated, but C, W, X and Y were all present [9]. Outbreaks in Burkina Faso in 2012 and Nigeria in 2013-2014 caused by serogroups W and C respectively suggest that increased surveillance is needed along with consideration of immunisation with multivalent conjugate vaccines rather than for *Neisseria meningitidis* group A alone [69, 70].

2.4.4 Immunity after vaccination

Assessment of the safety and immunogenicity of the vaccine has shown a 4-fold increase in serum bactericidal antibody (SBA) titers in 96% of the 601 subjects that took part in clinical trials in Mali and Gambia [71]. Studies conducted in the first years after MenAfriVac introduction showed more than 90% of vaccinated individuals maintaining high antibody titers against NmA [72]. Four years after vaccination, 90% of the subjects are still considered protected against NmA [73].

As years go by and new data are being collected, scientists begin to assess the duration of vaccine-induced protection. Tapia *et al.* in 2015 estimated that a single dose administrated to children aged less than two years provides protection against NmA for up to five years [74]. A more recent study shows that older age is associated with better antibody persistence and hence protection lasts longer when children receive a dose at the age of five years or older compared to being vaccinated when they are less than 5 years old [75]. More specifically, data from two randomised trials were used and analysed. The first trial included children aged between 12 and 23 months while the second randomised trial included participants aged 2-19 years. Immunogenicity was assessed with a serum bactericidal antibody (SBA) assay as well with MenA-specific immunoglobulin G (IgG) enzyme-linked immunosorbent assay (ELISA). The study aims to make predictions about vaccine efficacy in the next 20 years. Twenty years after primary vaccination, vaccine

efficacy is predicted to be 70% among people aged between 2-29 years compared to 52% in those in the 12-23 months age group. The authors of the paper translated these findings to a half-life of antibody persistence of 7.4 years for the younger age group and 16.5 years for the older participants, when measured by SBA titers. When measured by ELISA, the half-life was 4.5 and 6.3, respectively. According to this new study, ten years of duration of protection may be an underestimate and the true duration is potentially much longer. Another study, however, after conducting surveys in 2013 and 2016 in Burkina Faso, suggested that protection is shorter [76].

2.5 Using mathematical models to guide public health action

The mathematical modelling of human diseases dates back to the beginning of the 20^{th} century, when the first compartmental model was developed [77]. Technology has since advanced and has allowed the management of complex models and abundant sources of data. Computational models have become an essential tool for vaccine policy makers and they play an essential role in guiding public health actions.

The pioneer of the world's first vaccine was Edward Jenner in 1796 [78]. Jenner developed a vaccine to fight smallpox. The eradication of smallpox and the decline in incidences of other vaccine-preventable diseases such as polio and measles are testimonies to the effectiveness of vaccine interventions. The evaluation of public health programmes is not always possible with controlled trials. An evaluation, however, is essential to ensure that the expected benefits will happen using the most cost-effective means [79].

Mathematical modelling is a powerful tool to investigate the impact of a wide range of vaccination strategies on the epidemic patterns before they are implemented. The predictive scope of an epidemic model allows us to make projections of the incidence and prevalence of disease in both the vaccinated and unvaccinated population. Estimates of the impact of a vaccine on disease burden can then be used in cost-effectiveness models to assess the value for money that vaccination strategies offer in comparison to other potential health spending options. Cost-effectiveness studies are becoming a vital part of decision making process for many organisations, such as Gavi, the Vaccine Alliance and the Bill and Melinda Gates Foundation when considering the funding of new public health interventions. More specifically, Gavi builds the Vaccine Investment Case (VIS) based on the assessment of the potential impact of new vaccines generated by mathematical

models. This assessment takes place every five years and enables evidence-based decisions about future vaccine investments.

2.5.1 Models related to meningococcal infection

A number of meningococcal transmission models have been developed to date. Trotter *et al.* [19] developed a model attempting to estimate the forces of infection and risk of disease given infection for serogroups B and C using data from the late 1980s and early 1990s. The same group of researchers in 2005 published their work on the dynamic model of meningococcal carriage and the impact of serogroup C vaccination [80]. A few years later, in 2013, when a new vaccine against meningococcal disease was licensed in the EU, Christensen *et al.* [81] used two mathematical models to study its potential impact: a cohort model and a transmission dynamic model.

Any mathematical model attempting to specifically examine NmA transmission in the African meningitis belt should be able to capture the unique epidemiology the disease exhibits in that region. There are sporadic, unpredictable epidemics of different sizes and magnitudes occurring every 8-12 years taking place only during dry seasons. Irving *et al.* [82] developed a range of simple deterministic compartmental models of meningococcal disease and carriage to examine the importance of population immunity against the acquisition of the bacteria and also to explore how seasonality in transmission rates affected the model dynamics. Seasonal forcing and different assumptions regarding immunity were incorporated into the simple models. Irving *et al.* concluded that waning immunity and an increase in the risk of acquisition of carriage could play an important role in the occurrence of repeated epidemics at irregular intervals. A systematic review and meta-analysis of studies performed in 2015 suggested that seasonal changes in the rate of progression to disease should be taken into consideration in mathematical models of NmA transmission [83].

In 2013, Tartof *et al.* [84] developed an age-structured mathematical model of NmA transmission and used it to evaluate the impact of different vaccination strategies. Seasonality together with stochasticity were incorporated into their model. Despite the limited data and lack of model fit, their model was able to reproduce realistic patterns of the disease. This was the first mathematical model that supported the decision making about a long-term vaccination strategy in the countries introducing MenAfriVac. According to Tartof *et al.* the most effective long-term plan is to have periodic mass campaigns taking place every five years targeting children between the ages of 1 and 5 years. Jackson *et al.* revisited this model in 2018 [85] and used more recent published

studies to estimate parameters. In addition to updating parameter values, they examined the effect of key structural assumptions. Both models, the original [84] and the updated [85], suggest that a long-term immunisation strategy is essential in maintaining low levels of disease transmission.

Yaesoubi *et al.* [86] developed a stochastic compartmental model to investigate the cost-effectiveness of using a novel conjugate vaccine which would target more serogroups instead of just group A. The impact of alternative strategies involving the new vaccine are compared to the current strategy with MenAfriVac. Despite the limitations of the model and the uncertainty around assumptions made, they conclude that further immunisation with the novel vaccine will be cost-effective and will also lead to even more cases of meningitis averted.

Chapter 3

A mathematical model of meningococcal disease in Africa

3.1 Introduction

In this chapter, I extend the transmission models of Irving *et al.* [82] by addressing some of the limitations (including the assumption of homogeneous mixing, lack of age structure and the wide parameter space considered) and I incorporate vaccination. I will discuss how I formulate a model and utilise recently available NmA/MenAfriVac specific parameters. I will then apply the model to investigate appropriate vaccination schemes for the sustained use of MenAfriVac.

3.2 SCIRS model

This section introduces Irving *et al.*'s model version of $SCIRS^{CI}$ [82] that I am going to extend later. From the four structures Irving *et al.* explored, this one best describes the observed epidemiology of *Neisseria meningitidis* A in the African meningitis belt. We can think of the population being divided into four distinct compartments which represent their health status with respect to meningitis infection. An individual can be susceptible to infection (S), carrier of NmA (C), case of invasive meningococcal meningitis (I), or have temporary immunity from previous infection (R). Individuals carrying the bacteria show no signs of invasive disease but are infectious.

People are being born in the susceptible compartment. When there is contact between a susceptible and an infected individual, either a carrier or a case of invasive disease, the

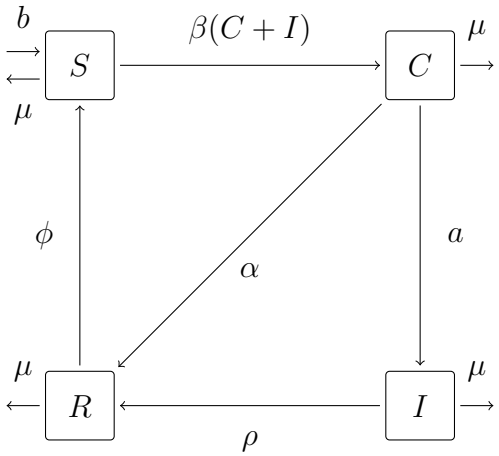

Fig. 3.1 Flow diagram of the SCIRS compartmental model. Individuals are divided into susceptibles (S), carriers (C), infected with meningitis (I) and recovered with temporary immunity (R). The arrows indicate possible movement to and from each compartment. β is the transmission rate. Carriers recover at a rate α or may develop invasive disease at a rate a. Infected individuals recover at a rate ρ. Temporary immunity wanes at a rate ϕ. b and μ are the birth and mortality rates, respectively.

susceptible may become a carrier. Once in the carriage state, one can either develop invasive disease or recover and have temporary immunity before they are moved back to the susceptible compartment. There is only movement to the recovered state for infected individuals. From each compartment there is a natural death rate μ. Since during epidemics only a small proportion of people develop invasive disease, and mortality rate is only 10%, deaths from disease are negligible compared with deaths from other/natural causes and, therefore, I altered the published model and assume that disease-induced death rate (γ) is equal to zero. The flow diagram of the simple SCIRS model can be seen in Figure 3.1 and a list of parameter names with their description is given in Table 3.1.

The SCIRS model is defined by the set of differential equations:

$$\begin{aligned}
\frac{dS}{dt} &= bN - \beta S\frac{(C+I)}{N} + \phi R - \mu S \\
\frac{dC}{dt} &= \beta S\frac{(C+I)}{N} - (a+\alpha+\mu)S \\
\frac{dI}{dt} &= aC - (\rho+\mu)I \\
\frac{dR}{dt} &= \alpha C + \rho I - (\phi+\mu)R,
\end{aligned}$$

Parameter name	Description
b	Birth rate
μ	Natural death rate
β	Transmission rate
ϕ	Rate of loss of immunity
α	Rate of loss of colonisation
a	Rate at which carriers develop disease
ρ	Recovery rate

Table 3.1 Parameter names and meanings used in this chapter.

where N = S+C+I+R. The total population N can be normalised to 1, so that S, C, I and R are fractions of the total population. The rescaled system is:

$$\begin{aligned}
\frac{dS}{dt} &= b - \beta S(C+I) + \phi R - \mu S \\
\frac{dC}{dt} &= \beta S(C+I) - (a+\alpha+\mu)S \\
\frac{dI}{dt} &= aC - (\rho+\mu)I \\
\frac{dR}{dt} &= \alpha C + \rho I - (\phi+\mu)R,
\end{aligned}$$

3.3 Derivation of the age-structured model for Burkina Faso

The vaccination campaigns with MenAfriVac target all individuals from 1 to 29 years of age, as discussed in section 2.4.2. In order to explore the effects of vaccination that targets specific age groups, an age structure needed to be added to the model described in the previous section [82].

I split the population into 19 age groups: 0 to <3 months, 3 to <9 months, 9 to <12 months, 1-4 years, 5-9 years, and 5-year age groups to age 80 years subsequently. This age grouping was chosen because there is high observed incidence in infants and toddlers and high carriage prevalence among children and young adults. Furthermore, the vaccination strategies explored in this chapter are mainly focused on the immunisation of infants and children.

The countries of the meningitis belt have rapidly growing populations, with a median age of 17 years in Burkina Faso [87]. The demographic part of this model is intended to correspond to the structure of the population of such a country. Annual fluctuations in the birth and death rates are not included since that would lead to a much more complicated model. Moreover, it would not be possible to know whether the observed features of meningococcal meningitis are due to epidemiological reasons (e.g levels of humidity) or annual demographic changes. The model presented here is developed for the population of Burkina Faso, a typical country in the region and entirely within the meningitis belt, and the demographic data used in simulations were chosen for 2011 or the closest available year.

The population growth rate for 2011 was estimated by the US Census Bureau as 3.09% per year [88]. The age-specific mortality rates were taken from the WHO's Global Health Observatory [89]. It is also assumed that all individuals die by the age of 80 and thus, the mortality rate of the age group 75-79 years is taken to be 0.2/year. In order to derive the age-structured demographic model of Burkina Faso, a method from Hethcote [90] was adapted by Irving. Full details of the method are in Tom Irving's PhD thesis and can also be found in Appendix A in this thesis. The age distribution used is shown in Figure 3.2. The simulated population seems to be a reasonable approximation of the actual distribution.

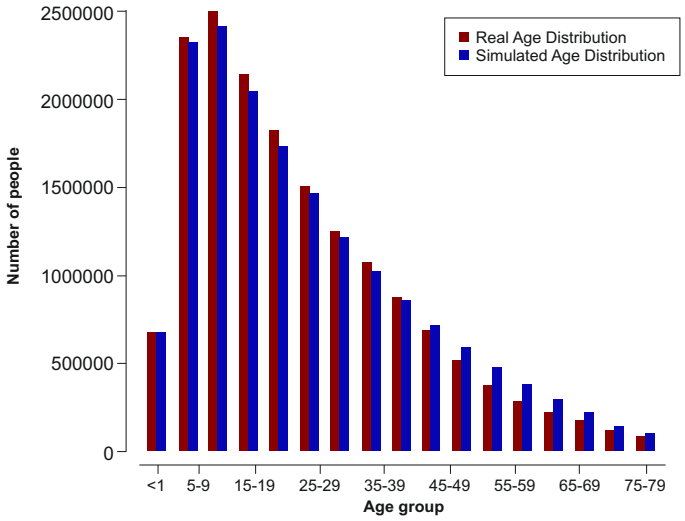

Fig. 3.2 Barplot showing the actual (red, taken from [88]) and simulated (blue) number of people in each age group. The data is for Burkina Faso for the year 2011.

The population distribution is taken to be stationary, that is, although the number of people in each age group increases exponentially, the proportion of the population in each age group remains constant.

The complete age-structured SCIRS model is given by the following system of coupled ordinary differential equations:

$$\text{for } j = 2, \ldots, 19$$

$$\frac{dS_1}{dt} = (K_1 + d_1 + q)P_1 + \phi R_1 - \lambda_1 S_1 - (K_1 + d_1 + q)S_1 \tag{3.1}$$

$$\frac{dS_j}{dt} = K_{j-1}S_{j-1} + \phi R_j - \lambda_j S_j - (K_j + d_j + q)S_j \tag{3.2}$$

$$\frac{dC_1}{dt} = -(a + \alpha)C_1 + \lambda_1 S_1 - (K_1 + d_1 + q)C_1 \tag{3.3}$$

$$\frac{dC_j}{dt} = K_{j-1}C_{j-1} - (a + \alpha)C_j \tag{3.4}$$

$$\frac{dI_1}{dt} = aC_1 - \rho I_1 - (K_1 + d_1 + q)I_1 \tag{3.5}$$

$$\frac{dI_j}{dt} = K_{j-1}I_{j-1} + aC_j - \rho I_j - (K_j + d_j + q)I_j \tag{3.6}$$

$$\frac{dR_1}{dt} = \rho I_1 + \alpha C_1 - \phi R_1 - (K_1 + d_1 + q)R_1 \tag{3.7}$$

$$\frac{dR_j}{dt} = K_{j-1}R_{j-1} + \rho I_j + \alpha C_j - \phi R_j - (K_j + d_j + q)R_j \tag{3.8}$$

where λ_j is the force of infection for the j^{th} age group and is given by

$$\lambda_j = \theta \sum_{k=1}^{n} \beta(z_j, z_k)(I_k + C_k) \tag{3.9}$$

The form of the matrix of contact rates between people in age group j and age group k $\beta(z_j, z_k)$ and the role of the stochastic term θ are discussed in Section 3.3.1 and 3.3.5, respectively. Seasonality is also implemented in the model and is be discussed in Section 3.3.2.

Parameter	Parameter Name	Value	Unit	Source
Size of the first age group	P_1	0.01	proportion	Census reports
Mortality rate	d	Age-specific (0.001-0.2)	$year^{-1}$	Census reports
Recovery rate from disease	ρ	52	$year^{-1}$	[3]
Rate of loss of carriage	α	12	$year^{-1}$	[25]
Transmission rate	β_0	10.5	$year^{-1}$	Estimate
Rate at which carriers fall ill	a	Age-specific (0.002-0.155)	$year^{-1}$	[83],age-specific parameters estimated
Rate of loss of immunity	ϕ	0.0839	$year^{-1}$	Estimate, based on [82]
Seasonal forcing of transmission rate	ϵ_β	0.6	-	Estimate, based on [82]
Seasonal forcing of invasion rate	ϵ_α	0.6	-	Estimate, based on [82]
Annual growth rate	q	0.0309	$year^{-1}$	Census reports
Rate of progression between age groups	K	Age-specific (0-3.94)	$year^{-1}$	Estimated using μ and q

Table 3.2 Model parameter names and values used for the model simulations. A range is given inside brackets for the age-specific parameters. Exact values can be found in Appendix A.

3.3.1 Mixing of population

The WAIFW (Who Acquires Infection From Whom) matrix is a central parameter in every age-structured epidemiological model. The WAIFW matrices describe the age-specific contact rates, $\beta(z_i, z_j)$, between individuals within and between different age groups. Several different WAIFW matrices were used and compared in preliminary analysis (following Tom Irving's PhD thesis, University of Bristol 2013). However, none of the matrices used by Irving were able to reproduce the observed age profiles of MenA carriage and disease in the African meningitis belt. In all the model simulations, the prevalence of carriage in young children and people aged more than 30 years was unrealistically high. As shown in Figure 3.3, carriage prevalence peaks in children and young adults while it drops in older ages. Unlike the observed patterns of carriage, 75% of all MenA cases are seen in children under the age of 15 years, while more than 40% of cases are in children younger than five years old [46].

A variation of the preferential mixing pattern is shown in Figure 3.4. People are assumed to interact more with people close to their age (b_2). Higher contact rates are assumed among children $>$ 5 years and teenagers to account for sibling contacts and

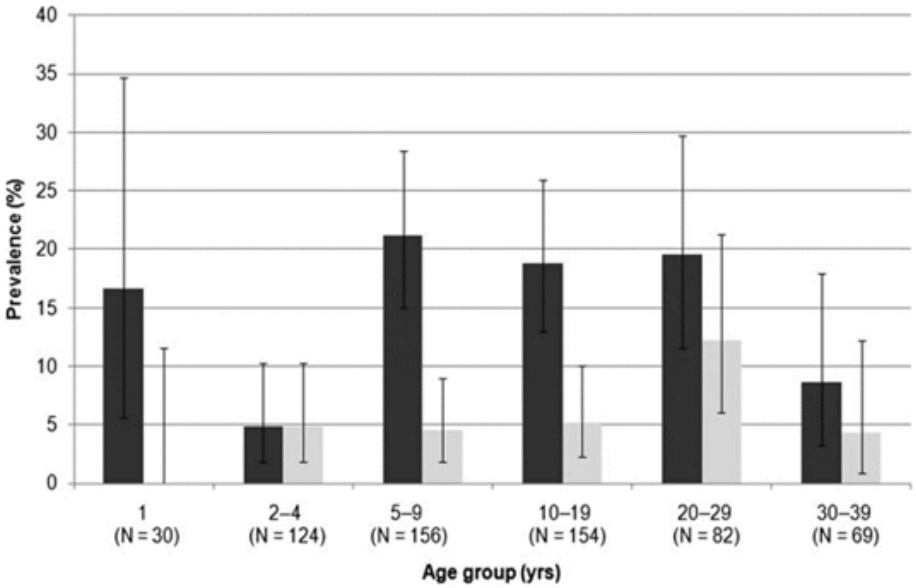

Fig. 3.3 Prevalence of serogroup A (dark grey) and serogroup Y (light grey) meningococcal carriage by age groups in the general population during a localized epidemic due to meningococcal serogroup A in western Burkina Faso, 2006. Error bars are 95% confidence intervals. Image from Mueller *et al.* [47].

school contacts (b_3). Also, since some of the risk factors of meningococcal disease is cigarette smoking and attendance in bars and clubs, high contacts are also assumed among people 15-30 years (b_4). The level of contact between all other age groups, b_1, is the lowest. For simplicity, it is assumed throughout that $b_2 = 2b_1, b_3 = 4b_1$ and $b_4 = 6b_1$.

I used the contact matrix shown in Figure 3.4 and I numerically solved equations (3.1)-(3.8) for different lengths of immunity, ϕ using the R package version 3.1.0, using the package deSolve. The range of ϕ explored was 5-12.5 years. As initial conditions, I assumed that 1% of the population is in the carriage state, 70% of the population are in the recovered compartments and the rest are assumed to be susceptible. I set the model to run for a period of 50 years, following a 20-year burn-in period, and record the age distribution of carriers and people infected with meningitis during one epidemic year. This was done in order to check that the model is able to reproduce realistic patterns of the age profile of carriage and disease.

Figure 3.5 shows the predicted age distribution of carriers (left) and disease (right) for three different values for ϕ. The results indicate that the profile of the age-distribution of carriage is a good visual fit as carriage is highest in teenagers. However, the predicted age profile of disease is not realistic. The proportion of cases in people over the age of

30 years is higher than expected. Natural immunity develops with age from repeated carriage episodes [19]. For that reason, the use of an age-dependent rate at which carriers fall ill (case: carrier ratio, a) is clearly important. I deal with this by varying the value of a as a function of age (see Table 3.2, exact values given in Appendix A)

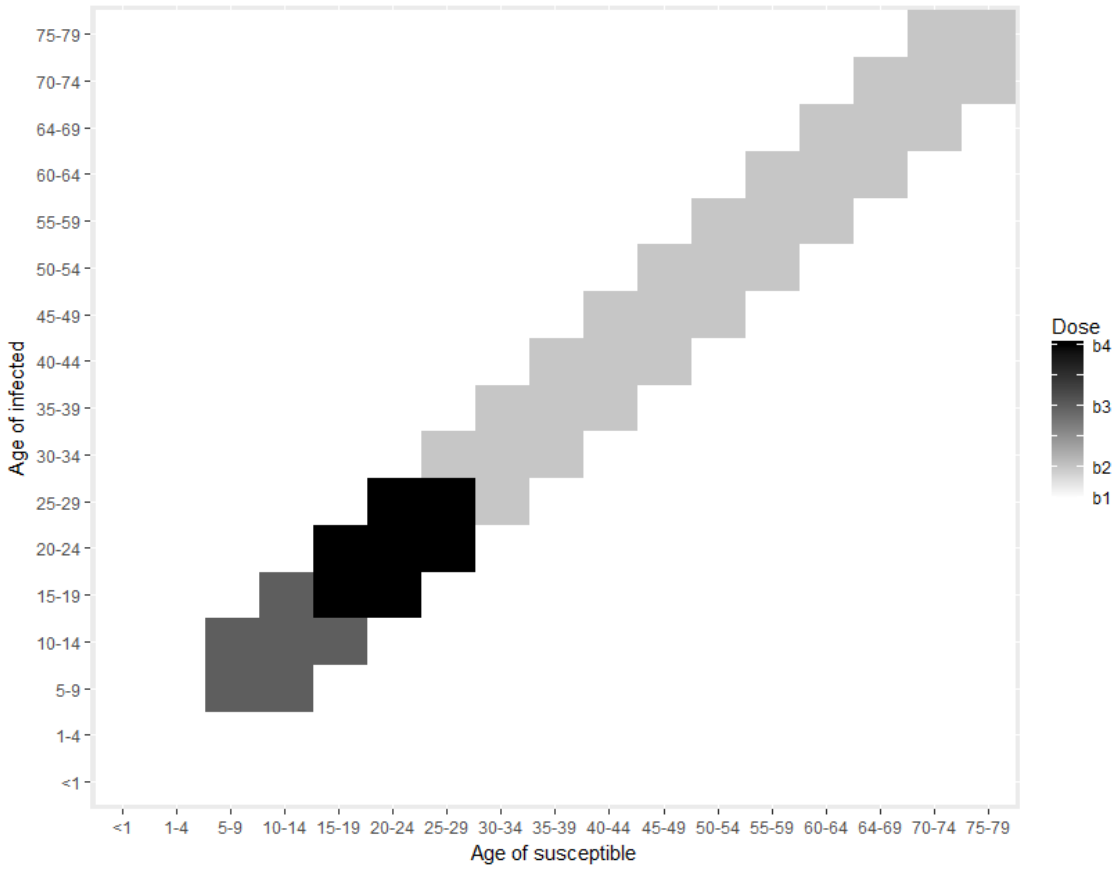

Fig. 3.4 Adapted WAIFW matrix. The boxes represent the contact levels between age groups. Darker areas represent higher contact rates. It is assumed that $b_2 = 2b_1, b_3 = 4b_1$ and $b_4 = 6b_1$.

3.3.2 Seasonality

Seasonality is a key feature of the epidemiology of MenA in the African meningitis belt. Every year from December to June, during the dry season, meningococcal disease incidence peaks and only dies out with the onset of the rains. Any mathematical model aiming to study the dynamics of meningitis infection in Africa should therefore incorporate seasonality in some way.

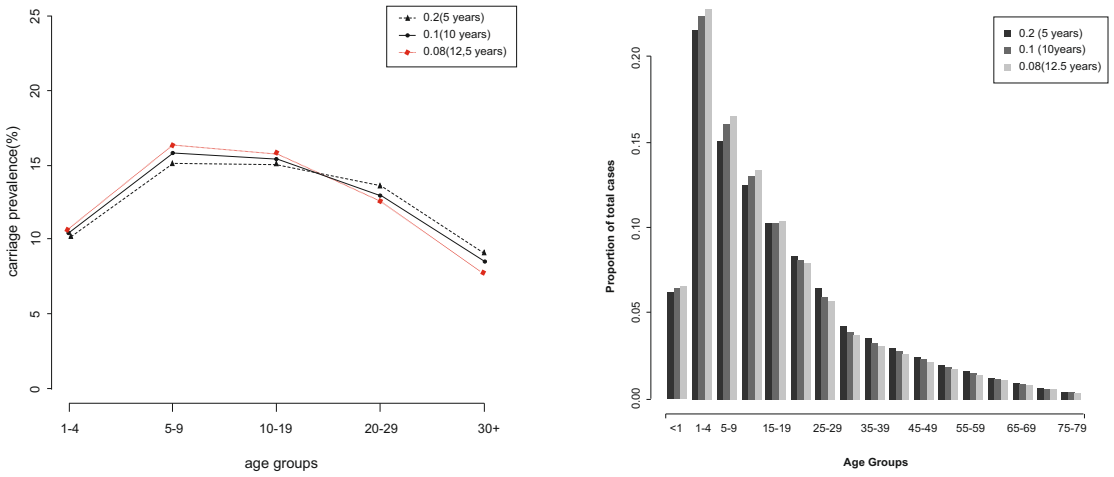

Fig. 3.5 Age profiles of carriage and disease simulated using the adapted WAIFW matrix. Left panel: Predicted carriage prevalence by age during an epidemic peak for three different values for the duration of temporary immunity. Right panel: Age distribution of cases during an epidemic peak for three different values for the duration of temporary immunity.

In this model, a sinusoidal term is used to capture the effects of seasonal change [82]. The transmission rate between people in the i^{th} and j^{th} age classes is defined as follows:

$$\beta(z_i, z_j) = \beta_0(z_i, z_j)(1 + \epsilon_\beta cos(2\pi t))$$

where ϵ_β scales the magnitude of the flunctualtion and β_0 is the baseline parameter value. Further, it is assumed that the seasonal variation in serogroup A meningococcal meningitis between the dry and the rainy season is driven by seasonal change in the ratio of clinical cases to carriers [83]. For that reason, the invasion rate is also replaced with a sinusoidal term as follows:

$$a(z) = a_0(z)(1 + \epsilon_a cos(2\pi t))$$

where ϵ_a scales the magnitude of the fluctuation and a_0 is the baseline parameter value.

3.3.3 Determination of parameters

Many model parameters are readily available in census reports and the scientific literature for most populations. Fertility and natural mortality rates are typically provided via recorded figures in census reports. Demographic rates and age distributions do not vary drastically when comparing less developed countries.

There are many parameters, however, that are not readily available in literature, such as effective contact rate (β) and rates at which carriers develop invasive disease (a). These rates, along with the number of individuals in each epidemiological stage, determine the age-specific force of infection and therefore, the horizontal spread of infection. Irving *et al.* [82] explored a wide range of values for the duration of natural immunity, ϕ, ranging from 6 months to 25 years. Their work showed that longer periods of immunity led to longer inter-epidemic periods similar to the observed epidemiology of *Neisseria meningitidis* group A in Bourkina Faso. For this reason, a range of 5 to 12.5 years is considered for the duration of natural immunity following a period of carriage or disease ($1/\phi$) in this model.

The number of unknown parameters makes it difficult to fix the rates at specific values, since the value of some rates affect the values of other unknown rates. The ABC (Approximate Bayesian Computation) method was used in an attempt to estimate some of the parameter values [91]. I attempted to fit parameters to the annual incidence of cases from Chad between 1930 and 2011. Although no clear estimates where given from the method, a strong correlation between the transmission rate and the duration of colonization was observed. This provided reassurance that the method was working to an extent, but was likely limited by the paucity of information within our chosen metric (i.e. annual meningitis incidence). These results from the ABC also gave good agreement with a not very large Basic Reproduction Number.

The baseline parameter values used for the numerical simulations of the model used throughout this chapter and the sources from which they were extracted are shown in Table 3.2.

3.3.4 Basic Reproduction Number (R_0)

I estimated the basic reproduction number by calculating the largest eigenvalue of the next-generation matrix [92]. That is, a matrix with elements $g_{ij} = \kappa S_i b_{ij}$, where g_{ij} is equal to the number of secondary infections in group i produced by an infective in group j, κ is the average duration of infectiousness ($1/\alpha$), S_i is the number of susceptibles in the i^{th} age class and b_{ij} is the transmission rate between age classes i and j. Since both the transmission rate and the duration of infectiousness are unknown parameters, R_0 was calculated for a number of parameter sets which reproduce 'realistic' results. It was found that the likely average value of R_0 is in the range 1.55 – 1.80.

3.3.5 Incorporating stochasticity into the model

Other factors that are not captured in the mechanics of this model may also be important and it is possible that there is variability in the parameters due to some unpredictable force. For example, the transmission rate may be modified by climatic conditions such as fluctuations in temperature or humidity; this may vary from year to year and so not be captured by the sinusoidal seasonal fluctuations. Such variability may be independent of carriage/disease prevalence or the number of susceptibles. For these reasons, I considered it important that stochasticity is taken into account and incorporated into the model. One modelling technique to introduce noise is to consider the governing parameter, i.e. the transmission rate, to be noisy [93]. The force of infection for the j^{th} age group is given by:

$$\lambda_j = \theta \sum_{k=1}^{n} \beta(z_j, z_k)(I_k + C_k)$$

where $\beta(z_j, z_k)$ is the contact rate between people in the j^{th} and k^{th} age classes and θ is a number drawn randomly from a uniform distribution of 0.8 to 1.2.

The use of such a stochastic term is necessary to reproduce irregular epidemics if the duration of carriage is taken to be one month, in line with the only published estimate of the duration of NmA carriage [25].

3.3.6 Numerical simulations

Solving equations (3.1)-(3.8), using the parameters shown in Table 3.2 and setting initial conditions as discribed in Section 3.3.1, we get the proportion of individuals in each of the four compartments (susceptible, carrier, infected, recovered) at any time t.

To compare the model results with the known data on the number of cases recorded, I need to calculate the incidence of infection. I do this by aggregating the number of new infections over a one year time step. One typical model run is shown in Figure 3.6. The model can describe the typical annual incidence of meningitis in the pre vaccine era, with irregular epidemics of varying size. During epidemic years the incidence can exceed 100 cases per 100,000 individuals, compared to very low incidence levels between epidemics.

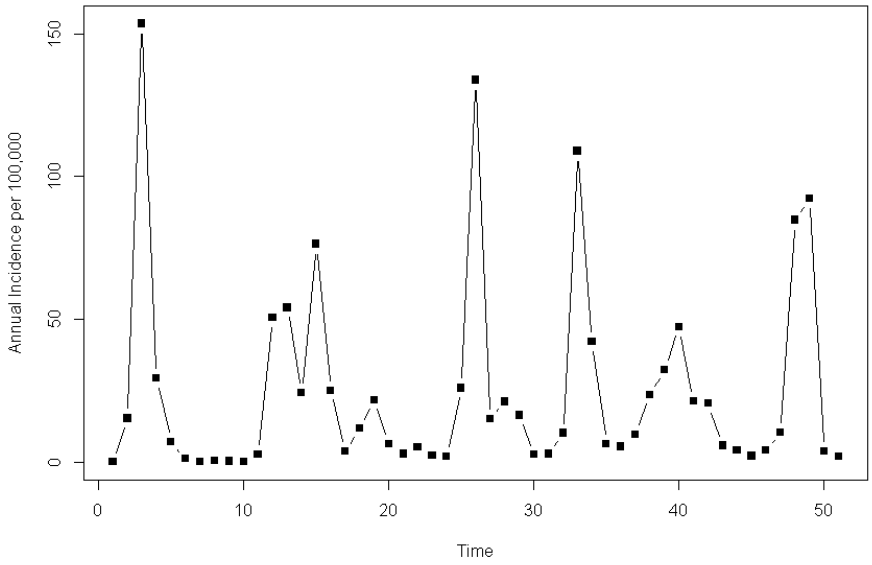

Fig. 3.6 Typical model results showing the annual incidence over a period of 50 years.

3.4 Vaccination

Based on their immunisation status with MenAfriVac, people are further divided into vaccinated and unvaccinated compartments. A schematic of the infection and vaccination processes can be seen in Figure 3.7. Note that births and deaths are not shown in the diagram but are included in the model. People are being born in the susceptible compartment and leave each compartment according to an age-dependent mortality rate.

Individuals enter the equivalent vaccinated compartments according the vaccination coverage ($v(z,t)$). Those in the vaccinated susceptible compartment are assumed to have some protection against aquiring NmA carriage (called vaccine efficacy against carriage, δ). A proportion of carriers (σ) is assumed to clear infection upon vaccination and enter directly the vaccinated immune state, while those who fail to clear carriage, are assumed to have some protection against developing invasive disease (called vaccine efficacy against disease, ξ). Vaccinated carriers who fail to recover immediately are assumed to recover at the same rate as unvaccinated individuals. Vaccinated individuals are assumed to revert to their equivalent unvaccinated compartment at a constant rate (w), due to the possible vaccine's failure to provide life-long protection.

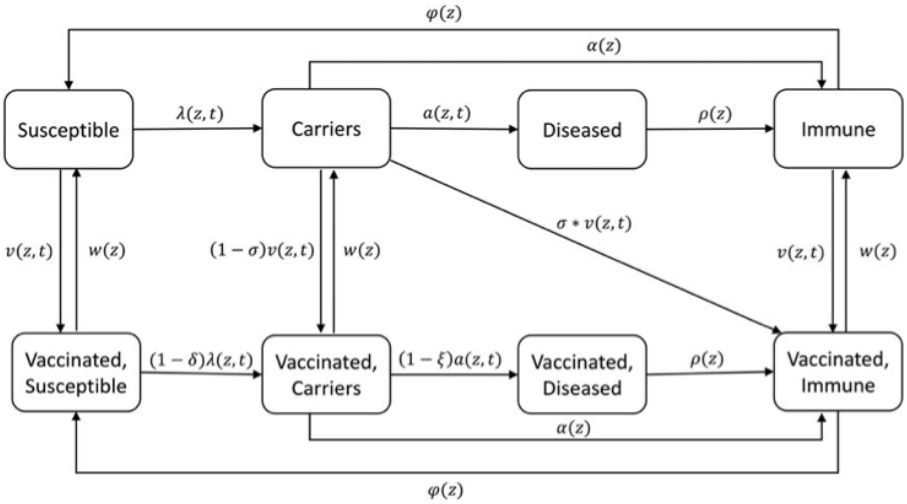

Fig. 3.7 Flow diagram of the SCIRS model with vaccination. Susceptible individuals become carriers at age and time dependent force of infection ($\lambda(z,t)$) which is reduced by the vaccine efficacy against carriage (δ) for vaccinated people. Similarly, the age and time dependent rate at which carriers develop disease ($a(z,t)$) is reduced by the vaccine efficacy against disease (ξ). Carriers and diseased individuals recover at a rate α and ρ, respectively. Temporary immunity wanes at a rate ϕ, while vaccine induced protection wanes at a rate w. Individuals are being transferred to the vaccinated compartments at a rate ν and σ is the proportion of carriers who loose carriage immediately upon vaccination.

The complete age-structured model with vaccination is given by the following system of coupled ordinary differential equations:

$$\text{for } j = 2, \ldots, 19$$

$$\frac{dS_1}{dt} = (K_1 + d_1 + q)P_1 + \phi R_1 - \lambda_1 S_1 - (K_1 + d_1 + q)S_1 \tag{3.10}$$

$$\frac{dS_j}{dt} = (1 - \gamma_{j-1})K_{j-1}S_{j-1} + \phi R_j - \lambda_j S_j - (K_j + d_j + q)S_j + wSV_j \tag{3.11}$$

$$\frac{dSV_j}{dt} = K_{j-1}SV_{j-1} + \gamma_{j-1}K_{j-1}S_{j-1} + \phi RV_j - (1 - \delta)\lambda_j SV_j -$$
$$(K_j - d_j + q)SV_j - wSV_j \tag{3.12}$$

$$\frac{dC_1}{dt} = -(a + \alpha)C_1 + \lambda_1 S_1 - (K_1 + d_1 + q)C_1, \tag{3.13}$$

$$\frac{dC_j}{dt} = (1 - \gamma_{j-1})K_{j-1}C_{j-1} - (a + \alpha)C_j + \lambda_j S_j + wCV_j \tag{3.14}$$

$$\frac{dCV_j}{dt} = K_{j-1}CV_{j-1} + \gamma_{j-1}K_{j-1}C_{j-1} - ((1 - \xi)a + \alpha)CV_{j-1} +$$

$$(1-\delta)\lambda_j SV_j - (K_j + d_j + q)SV_j - wCV_j \tag{3.15}$$

$$\frac{dI_1}{dt} = aC_1 - \rho I_1 - (K_1 + d_1 + q)I_1 \tag{3.16}$$

$$\frac{dI_j}{dt} = K_{j-1}I_{j-1} + aC_j - \rho I_j - (K_j + d_j + q)I_j \tag{3.17}$$

$$\frac{dIV_j}{dt} = K_{j-1}I_{j-1} + (1-\xi)aCV_j - \rho IV_j - (K_j + d_j + q)IV_j \tag{3.18}$$

$$\frac{dR_1}{dt} = \rho I_1 + \alpha C_1 - \phi R_1 - (K_1 + d_1 + q)R_1 \tag{3.19}$$

$$\frac{dR_j}{dt} = (1-\gamma_{j-1})K_{j-1}R_{j-1} + \rho I_j + \alpha C_j - \phi R_j - (K_j + d_j + q)R_j + wRV_j \tag{3.20}$$

$$\frac{dRV_j}{dt} = K_{j-1}RV_{j-1} + \gamma_{j-1}R_{j-1} + \rho IV_j + \alpha CV_j - \phi RV_j - (K_j + d_j + q)RV_j - wRV_j, \tag{3.21}$$

where γ is the rate of routine vaccination, w is the rate of loss of vaccine induced protection, and δ and ξ are the vaccine efficacy against carriage and disease, respectively. The values of the parameters characterising disease are taken to be the same as in Table 3.2, while Table 3.3 includes the values of the vaccine associated parameters under the base case scenario as well as the full range explored in the sensitivity analysis.

Parameter	Name	Value	Range	Unit	Source
Vaccine efficacy against carriage	δ	0.9	0.6-0.9	Proportion	[10]
Vaccine efficacy against disease	ξ	0.9	0.6-0.9	Proportion	[10]
Carriage clearance upon vaccination	σ	0.9	0-1	Proportion	-
Waning of vaccine protection	w	0.1		years^{-1}	-
Vaccine coverage for initial mass campaign		0.95		Proportion	[59, 62]
Vaccine coverage for additional mass campaigns		0.8	0.6-0.8	Proportion	-
Vaccine coverage for routine EPI	ν	0.8	0.5-0.8	Proportion	-

Table 3.3 Vaccine associated parameters under the base case scenario. Range explored in a sensitivity analysis

When this work was conducted and published, there had been no studies assessing the duration of protection induced by MenAfriVac. An average of 10 years duration of

protection was chosen as the baseline parameter value, consistent with findings from unpublished Meningitis Vaccine Project (MVP) trials which is further explored in a sensitivity analysis in Chapter 6. Similarly, due to limited data at the time, the range for routine vaccination was taken from typical Expanded Programme on Immunisation (EPI) coverage in meningitis belt countries.

3.4.1 Vaccination strategies

I considered a range of long-term vaccination strategies and compared them to a scenario without any vaccination and with only an initial mass vaccination campaign of 1-29 year olds. I simulated the introduction of MenAfriVac into the Expanded Programme on Immunisation (EPI), which is routine immunisation of infants less than 12 months old. Vaccination through EPI takes place when a child reach a specified target age. In addition to routine immunisation of infants, I also simulated periodic mass vaccination campaigns, targeting people born since the last mass campaign; either 1-4 year olds every 4 years or 1-9 year olds every 9 years. Finally, I simulated a combination strategy whereby MenAfriVac was introduced into EPI five years after the initial campaigns had taken place, with a catch-up campaign of 1-4 year olds. The catch-up campaign intends to target the children who were either not born at the time of the introduction or they were too young to be immunised then.

The full range of vaccination strategies considered are summarised in Table 3.4.

3.4.2 Model implementation

The model was coded and run using the R software version 3.1.0 [94], using the package deSolve to perform the numerical integration of differential equations. The time step was 1 day. For each simulation, I ran the model for a 20-year burn-in period before implementing the initial mass vaccination campaign in year 0. The model was then run for a further 40 years; all results are reported for this 40-year period. For each vaccination strategy, the average of 300 simulations was taken; this was based on a comparison of between 100 and 500 simulations that showed very small marginal differences between 300 and 500 simulations.

In the model, the initial campaign targeting 1-29 year olds is assumed to be a discrete time event at one point in time, and was implemented by transferring the individuals in the targeted age groups ($4^{th}, 5^{th}, 6^{th}, 7^{th}, 8^{th}$ *and* 9^{th}) to their corresponding vaccinated compartments at time $t = t_v$. In a similar way, periodic mass immunisations were also

Vaccine Strategy	Introduction	Long-term
A. Initial campaign only	Mass immunisation of 1-29 year olds	None
B. Periodic campaigns	Mass immunisation of 1-29 year olds	1. Periodic mass immunisation of 1-4 year olds every 4 years; 2. Periodic mass immunisation of 1-9 year olds every 9 years
C. Routine EPI	Mass immunisation of 1-29 year olds	Routine EPI months, 5 years after introduction
D. Combination	Mass immunisation of 1-29 year olds	Routine EPI, 5 years after introduction plus 1-4 year old catch-up

Table 3.4 Full range of vaccination strategies considered in the model runs

treated as discrete events and were implemented by transferring individuals from the fourth unvaccinated age group (1-4 years) to the corresponding vaccinated age group every five years. Routine immunization was implemented continuously as individuals reached the target age for the EPI. The narrow age groups in <1-year-olds allowed routine vaccination to be implemented at different ages.

3.4.3 Results

Following initial mass vaccination of 1-29 year olds at high uptake, disease control was excellent in the short term. With no subsequent immunisation, the model predicted a strong resurgence in disease incidence approximately 15 years after vaccine introduction, assuming an average of 10 years of protection by vaccination.

In the absence of any vaccination, the model predicted an average annual incidence of 24.5 cases per 100,000 population. After primary vaccination, incidence remains very low, <1/100,000 for approximately 15 years, followed by a rapid increase in disease incidence with a peak of 79 cases per 100,000 population, before it declines again to an equilibrium of 24.5 cases per 100,000 population. The trajectories of 300 model runs are plotted together with the mean in Figure 3.8, where a rapid increase in disease incidence can be clearly seen in all simulation runs.

Of the long-term immunization strategies considered, all were effective in maintaining control of disease as they all resulted in a lower average annual incidence compared to a scenario with only the initial mass campaign taking place. The predicted average annual

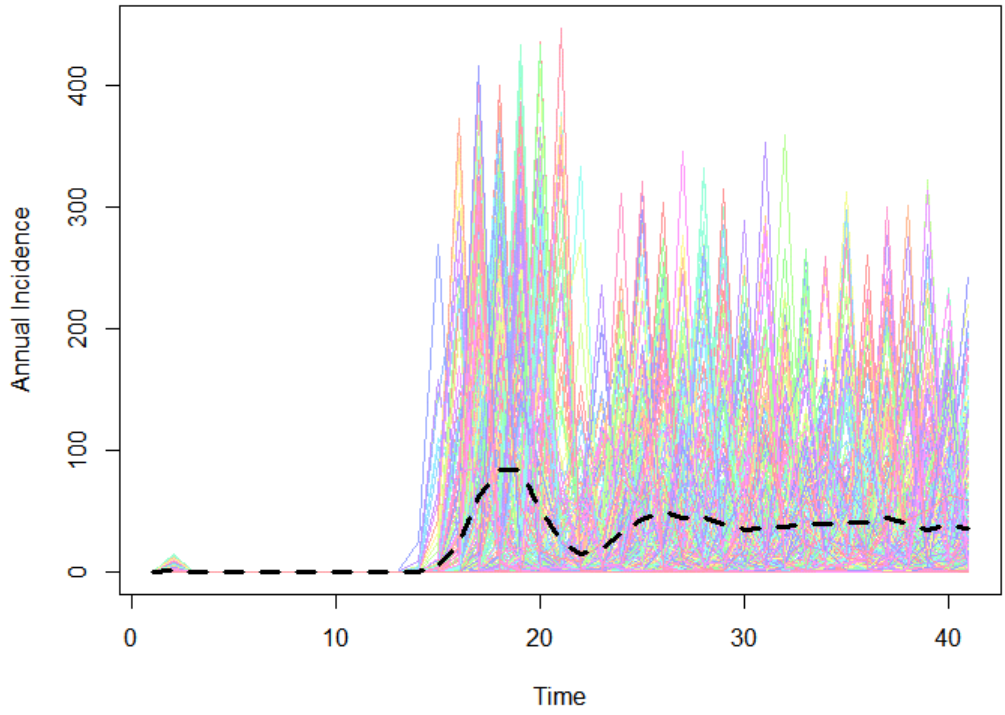

Fig. 3.8 Results from 300 simulations of the initial mass immunization of 1- to 29-year-olds (implemented in year 0). The black dashed line depicts the mean annual incidence.

incidence for the different scenarios can be seen in Table 3.5. There was considerable overlap in the distribution of results (Figure 3.9), but routine EPI immunization at 9 months of age (strategy C) resulted in lower average annual incidence than regular mass campaigns of 1 to 4-year-olds (strategy B) under base case assumptions. Note here that as strategy B in all the following figures, I will be referring to periodic mass campaigns of 1-4 year olds every 4 years. Strategy C was superior to strategy B provided that EPI coverage was above approximately 60%. The strategy with the lowest overall average annual incidence and longest time to resurgence was introduction into EPI at 9 months, 5 years after the initial mass campaigns, with a catch-up targeting unvaccinated children aged 1–4 years (strategy D). All the results are summarised in Table 3.5.

All long-term strategies resulted in disease incidence of less than 10 cases per 100,000 population. The periodic mass vaccination of 1 to 4 year olds every five years and the periodic mass vaccination of 1-9 year olds every 10 years following the primary campaign,

both resulted in an average annual incidence of around 7 cases per 100,000 population across the 40-year period. The two strategies were very close to each other, however, the mass vaccination of 1 to 9 year olds resulted in greater herd immunity, at the expense of toddlers between 1 and 4 years of age. In Figure 3.10, the strong resurgence in the absence of any long term strategy is highlighted. The strategy with the longest time to the next peak is the 'combination' strategy (i.e the black line in Figure 3.10).

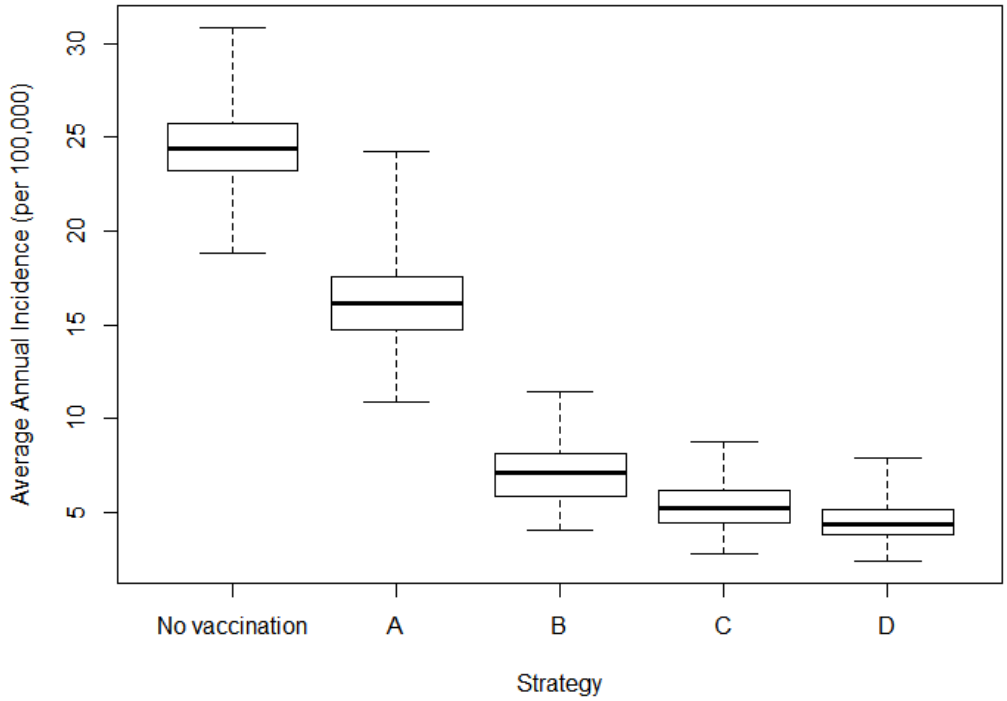

Fig. 3.9 Box plot to show the median, interquartile range, and full range of the predicted annual incidence per 100 000 for different immunization strategies in the 40 years following vaccine introduction from 300 model simulations. Strategy B refers to vaccination of 1-4 year olds every 4 years from Table 3.4.

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Assuming that 80% coverage could be achieved by both EPI and periodic mass campaigns, routine EPI vaccination was better than periodic mass vaccination campaigns (Figure 3.10). In fact, it appeared that EPI was superior to mass campaigns unless EPI coverage was very low (less than around 60%).

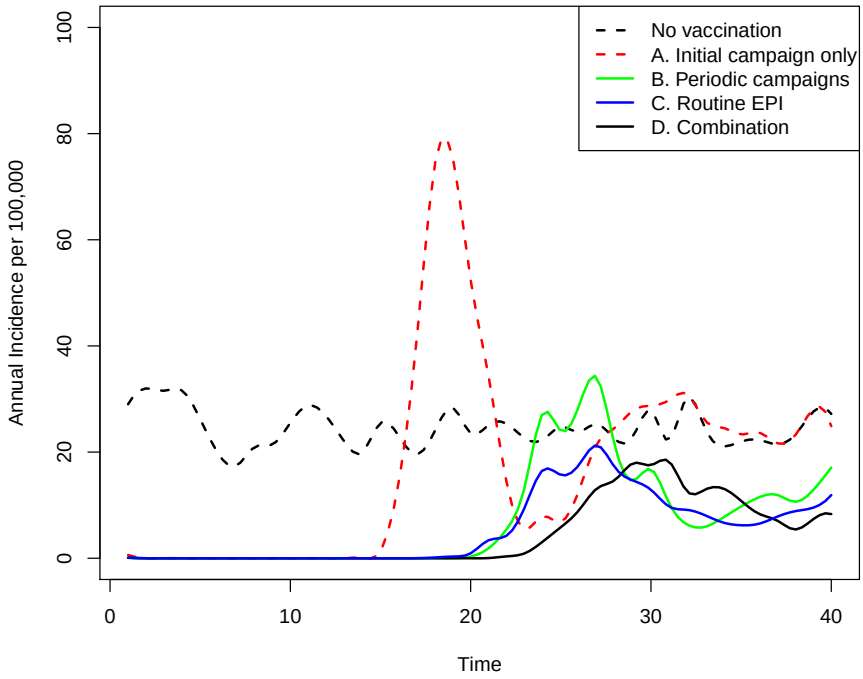


Fig. 3.10 Comparison of immunisation strategies under consideration. Different colour lines represent the mean annual incidence over a 40 year period after vaccination (implemented in year 0). Averaged across 300 simulation runs.

Age group	No Vaccination	Mass 1-29 Only	Mass 1-29 and EPI at 9m	Mass 1-29 and Periodic Campaigns of 1-4y	Mass 1-29 Plus EPI at 9m and 1-4y Catch-up
<1	40.32	27.71	8.77	13.52	7.50
1-4	37.38	25.82	4.43	7.15	3.80
5-9	42.54	28.76	6.92	10.00	5.91
10-14	38.61	26.82	8.71	11.48	7.43
15-19	32.14	23.05	9.96	12.10	8.51
20-24	19.18	14.06	7.05	8.26	6.07
25-29	11.20	8.36	4.36	5.10	3.80
30+	3.18	2.35	1.07	1.30	0.94
All	24.45	17.06	5.31	7.12	4.56

Table 3.5 Estimated average annual Neisseria meningitidis group A incidence per 100,000 by age group in the 40 years following vaccine introduction under different immunization strategies. Averaged across 300 simulation runs.

3.4.4 Sensitivity analysis

I investigated the effect of changing some key model parameters and assumptions. In the absence of any long-term immunization, assuming a shorter duration of protection resulted in disease incidence increasing more quickly; with 5 years of vaccine protection, the resurgence occurred after around 10 years.

Increasing the age of routine vaccination, from 0 to 3 to 9 to 12 months, I observed only marginal differences (see Figure 3.11), with overall disease incidence decreasing when immunising at older ages. However, there were more cases in infants as the age at routine immunisation increased (see Table 3.6). To allow for comparison, I assumed a fixed coverage of 80% for routine immunisation across all scenarios. When averaged across 300 simulations, when MenAfriVac was given routinely at the age of 3 months, the model predicts an average annual incidence of 5.43 cases per 100,000 population per year in all ages and 4.67 cases per 100,000 individuals in infants, compared with the base case of immunization at 9 months (average annual incidence of 5.31 cases/100,000 across all ages and 8.77 cases/100,000 in infants). Immunizing within EPI at 12 months of age results in an average annual incidence of 5.18 cases per 100,000 population, but 10.53 cases per 100,000 in infants.

Age group	EPI at 0 months	EPI at 3 months	EPI at 9 months	EPI at 12 months
<1	2.99	4.67	8.77	10.53
1-4	5.15	4.85	4.43	4.16
5-9	7.82	7.44	6.92	6.58
10-14	9.63	9.23	8.71	8.34
15-19	10.79	10.41	9.96	9.58
20-24	7.54	7.31	7.05	6.81
25-29	4.64	4.50	4.36	4.24
30+	1.13	1.10	1.07	1.04
All	5.59	5.43	5.31	5.18

Table 3.6 Average annual incidence per 100,000 people by age group for routine vaccination at different ages and coverage of 80%. Averaged across 300 simulation runs.

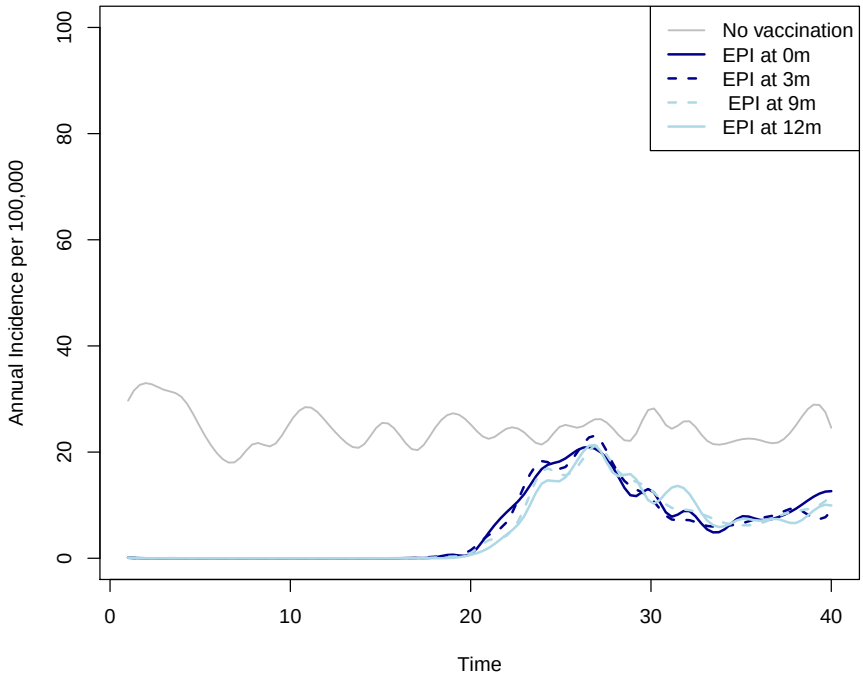


Fig. 3.11 Results from 300 simulations of the initial mass immunization of 1- to 29-year-olds (implemented in year 0) and routine EPI at birth, 3 months, 9 months or 12 months of age. The lines represent the mean across the 300 simulation runs. Coverage for routine EPI is assumed to be 80%.

As expected, as EPI coverage increased, the incidence of disease decreased. For every 10% increase, the average annual incidence decreases by approximately 1 case per 100,000 population per year. The time to the first peak is also longer when higher coverage is assumed. Results of routine immunization at 12 months of age under different assumptions for the coverage is shown in Figure 3.12.

The vaccine effectiveness against carriage and disease is not known. In the base case, I assumed that MenAfriVac offered a 90% protection against both disease and carriage. The model results were insensitive to changes in the assumption of vaccine effectiveness against disease (ξ) when vaccine effectiveness against carriage (δ) was high (90%). This can be explained because in this situation, carriage acquisitions were rare and therefore, few people were at risk of disease downstream. Because it is unclear whether the vaccine can clear an episode of carriage, I also investigated the sensitivity of the results to changes in clearance upon vaccination. In the base case, I assumed that 90% of the carriers

recover immediately after vaccination; when this proportion changed to 10%, I found that the results were insensitive to the change.

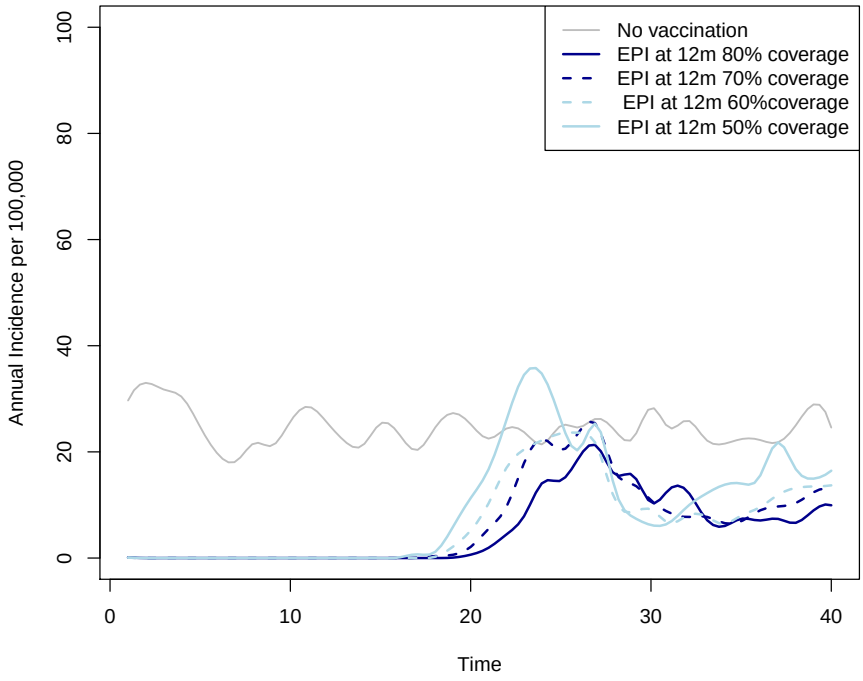


Fig. 3.12 Results from 300 simulations of the initial mass immunization of 1- to 29-year-olds (implemented in year 0) and routine EPI at different coverage levels. Lines represent the mean across simmulation runs.

One key parameter of the model which is not known is the duration of natural immunity after an episode of colonisation or disease. The assumption made under the base case scenario was that individuals are immune for an average of 12 years after they have cleared infection. When this was lowered to 7 years, keeping all other parameters fixed, the incidence of disease under all scenarios was higher. However, the relative ranking of each strategy did not change.

The sensitivity of the results to changes in the model structure were also investigated. In the base case, the stochastic term is a random number drawn annually. When I changed this to weekly, a wider range of numbers was necessary for the model to produce irregular epidemics. However, the results from the "noisy" model in which the transmission rate varied stochastically each week were very similar to the results presented here.

3.5 Discussion

I developed a model of NmA transmission and disease that was able to describe the epidemiology observed in the African meningitis belt. I simulated the impact of the initial mass vaccination campaigns of 1-29-year-olds and predicted a period of very low incidence for at least ten years, even when assuming a relatively short duration of protection. The indirect effects of the vaccine were crucial in maintaining this low incidence post-introduction; I considered a high degree of protection against carriage, consistent with the observed data [63, 10]. Following this honeymoon period, the model predicted a strong resurgence in disease incidence if there was no long-term immunisation strategy. Of the long-term strategies I investigated, a combination strategy of routine EPI vaccination after five years together with a catch-up campaign targeting children aged 1-4 years who were born after the initial campaigns was the most effective, although there was considerable overlap in the distribution of results for different strategies. Routine EPI alone appeared to be more effective than periodic mass campaigns, unless EPI coverage was less than approximately 60%.

These findings suggest, first, that it is essential to implement a long-term strategy for the continued use of MenAfriVac. It is not sufficient for the vaccine only to be used in a large one-off campaign, as this may result in catastrophic resurgences in disease 10-20 years after vaccine introduction. All of the long-term strategies considered were effective in maintaining disease control, although for all strategies incidence was predicted to rise over the long-term as population immunity from the initial campaign waned. The inclusion of MenAfriVac into the routine EPI as a single dose at nine months of age has the apparent advantage of using and likely strengthening existing infrastructure. The option to conduct periodic campaigns may, however, provide better disease control for those countries with very poor routine EPI uptake. The combination strategy of introduction into routine EPI with a one-off catch-up campaign targeting those born since the initial campaign was the most effective and also the most equitable option.

My work has several strengths and limitations. I based my model structure on extensive previous work that used a range of deterministic models, to explore the importance of seasonality and immunity following colonisation [82]. I extended these models to incorporate age structure and vaccination and included a stochastic term so that the extent of seasonal forcing varied from year to year, to capture the effect of external forces (including, e.g. dust or humidity conditions). I parameterised the model using appropriate published and unpublished data specific to African populations as far

as possible. Although Burkina Faso and the rest of the sub-Saharan countries have got an increasing annual growth rate, the use of a fixed rate in this instant is justified since I am only considering 40 years post-vaccination. For a longer time horizon, more realistic demographic parameters are essential to capture all demographic changes and their potential effect on the model results. Some model parameters were unknown including the transmission rate and duration of natural immunity. Here, I used a variety of methods to estimate a reasonable range and possible parameter combinations, ensuring that the model produced realistic results by comparing the model predictions to evidence on carriage prevalence by age, disease incidence by age, total annual incidence, seasonality, and periodicity. Further investigation of formal fitting methods such as Approximate Bayesian Computation is warranted, and more information on a range of parameters would be desirable, including age-specific contact patterns. Quantifying the duration of natural immunity following infections is particularly difficult; estimation is hampered by co-dependence with other parameters, and empirical measurement is problematic, not least because of the lack of an absolute correlate of protection [95]. I performed sensitivity analyses to investigate parameter uncertainty and showed that my findings were robust.

My conclusions are different from another model of MenAfriVac, which found that mass campaigns were superior to routine EPI. This is probably largely because the duration of protection assumed by Tartof *et al.* was much higher (essentially life-long) for children immunised in campaigns than through EPI [84], whereas I assumed that protection in 1-to-4-year-olds would be similar to those immunised at the age of 9 months, based on recent data from the MVP's MenAfriVac trials. Tartof *et al.* also used a different model structure, a larger time-step, non-continuous ageing, a smaller number of simulations, and higher frequency (weekly) and amplitude (0-0.75) of stochastic forcing. I chose a more parsimonious model structure that did not consider variable levels of protection against colonisation and disease, as there was little evidence to inform such a structure and its parameterisation. I explored the effect of other structural changes in my model, including the implementation of stochasticity as weekly variation in transmission rates, but this had minor impact on the model predictions and did not change my conclusions on the relative merits of each immunisation strategy.

The burden of disease predicted by the model for the first 26 years after introduction with MenAfriVac was used in a cost-of-illness study which showed that preventive immunisation with MenAfriVac would be significantly cost saving for Burkina Faso, compared with reactive, emergency mass vaccination campaigns [96].

Following its introduction in 2010, MenAfriVac has been remarkably successful in controlling NmA disease. This success will not be maintained without a long-term immunisation strategy. The early adopting countries will need to consider imminently how best to sustain population protection against NmA, and findings from mathematical models such as this can lend further support to decision makers at both the country level and internationally.

Chapter 4

Comparing to published mathematical model of MenAfriVac impact

4.1 Introduction

A mathematical model can be used to provide predictions, the validity of which relies on the underlying assumptions of the model [97]. "All models are wrong, but some are useful" is a famous quote by the British statistician George E. P. Box. A model is a mere approximation of reality. When developing a disease transmission model, one is forced to make assumptions regarding the inputs (i.e. the model parameters) as well as the structure of the model. Each assumption, however, is a source of uncertainty around the model outputs. The robustness of a model's results against assumptions around the inputs can be examined with sensitivity analysis [98, 99]. One way to examine the validity of a model and the trustworthiness of its predictions is by comparing it with other models. Model comparison is a common practice among researchers [100–103]. If two or more models using different mechanisms to describe disease transmission yield similar results, we gain some confidence in the predictions produced. However, different models may lead to similar observed patterns in the absence of vaccination but may fail to do so when intervention is added [97]. This can be due to different mechanisms governing the models. It can be beneficial, therefore, to have more than one model to address policy makers questions.

Up to the time of writing, two mathematical models have been published to support decision making about long-term vaccination strategies with MenAfriVac in the African meningitis belt. The first paper to be published was by Tartof *et al.* in 2013 [84] followed by the model presented in Chapter 3 which was published in 2015 [104]. The two models were developed independently and both aim to investigate the impact of different immunisation strategies with MenAfriVac. Both models considered the same selection of immunisation strategies as those were of interest to WHO and CDC at the time. Both are stochastic transmission models that can reproduce key features of the epidemiology of NmA in the African meningitis belt. But while the models use similar values for specific parameters, the models also differ in potentially important ways, including differences both in parameter values and in model structure. In consequence, the models make different predictions regarding the relative benefits of different NmA vaccination strategies. For that reason, I wanted to compare the two models and determine which assumptions influence these differences in predictions. By doing so, I hope to resolve/interpret differences in policy-relevant outcomes, identify areas for improvement and address important knowledge gaps.

4.2 Model Desrciption

4.2.1 Tartof *et al.* model

Model structure

The population is divided into different states based on age, level of protection (None, Low, High) and meningitis infection status (Susceptible, Carrier, Diseased). Individuals in the high protection state are assumed to have a very high level of immunity to becoming colonised, and if colonised, they cannot become diseased.

Individuals in the low protection state are assumed to have relatively low immunity to colonisation but still high protection against disease. The no protection state represents individuals with no immunity to colonisation or disease (Figure 4.1). It is further assumed that vaccination with MenAfriVac is equivalent to natural infection in inducing immunity to future colonisation and disease.

Implementation

The population is divided into 361 age groups by month of age with individuals 30 years and older treated as one homogeneous age group using census data to determine the age

distribution of Burkina Faso in 2010. The ageing process is discrete and individuals move from one age group to the next each month, while newborns enter the model at age a=0.

Seasonality is incorporated into the model by having two different Who Acquires Infection From Whom (WAIFW) matrices. One for the dry season, which runs from November through April, and one for the rainy season. Similarly, the rate at which colonised individuals develop invasive disease is higher during dry season compared to a lower value in the rainy season.

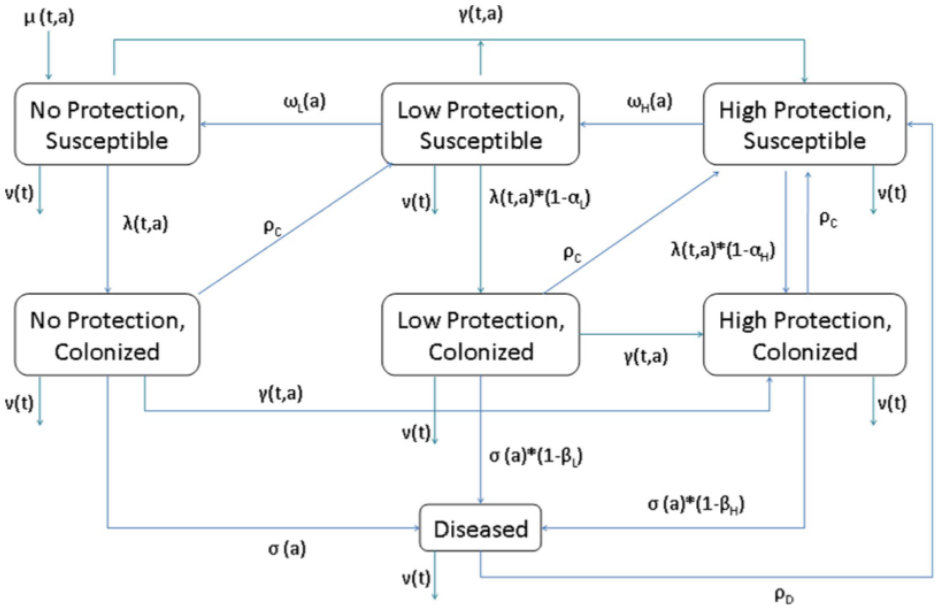


Fig. 4.1 Model diagram in Tartof *et al.* [84]. Individuals are born into the no protection, susceptible state with time- and age- dependent birth rate μ(t,a) and die from all model states with time-dependent death rate ν(t). Susceptible individuals become colonized at time- and age- dependent force of infection λ(t,a), which is reduced by immunity due to low (α_L) or high (α_H) protection levels. Colonized individuals develop invasive disease at age-dependent rate σ(a), which is reduced by low (β_L) or high (β_H) protective immunity. Diseased individuals recover to the high protection, susceptible state at recovery rate ρ_D, low protection colonized individuals recover from colonization to the high protection, susceptible state at recovery rate ρ_C, and no protection colonized individuals recover from colonization to the low protection, susceptible state at recovery rate ρ_C. Protection wanes from high to low and from low to none, at age-dependent rate ω_H(a) and ω_L(a), respectively. Susceptible individuals with no or low protection are vaccinated at time- and age- dependent rate γ(t,a), where vaccination induces high protection.

The transmission rate is multiplied by a stochastic term added to allow cyclic but irregular epidemics similar to observed epidemic patterns. The stochastic term ϕ is calculated as:

$$\phi = 1 + 0.75cos(\theta\pi)$$

where θ is a random number drawn from the uniform distribution (0,1) [1].

The model is governed by a set of stochastic difference equations that were numerically solved using a time step of one calendar week. All computations were implemented using SAS version 9.2.

4.2.2 Karachaliou *et al.* model

Model structure

This is a compartmental model that divides the population based on their infectious status. Individuals are assigned to one of the following states: (a) susceptible, (b) carrier of NmA, (c) disease due to NmA and (d) recovered and immune (Figure 3.7).

Implementation

The population is divided into 19 age groups, 0 to <3 months, 3 to <9 months, 9 to <12 months, 1-4 years, 5-9 years, and 5-year age groups to age 80 years subsequently, with continuous ageing between age groups. The proportion of the population in each age group remains constant over time.

Seasonality is implemented through seasonal forcing of the transmission rate and the rate at which carriers develop invasive disease using a sinusoidal function.

Stochasticity was introduced with annual variations in the transmission rates, drawn from the uniform distribution (0.8-1.2).

Vaccination was implemented in different ways according to the strategy used. Mass vaccination campaigns occurred as a discrete event at one point in time, whereas routine immunisation was implemented continuously as individuals reached the target age. It is assumed that the risk of transmission and the risk of developing invasive disease is lower among vaccinated individuals.

The model is governed by a set of stochastic differential equations that were numerically solved in R using the lsoda function in package deSolve [94] with a time step of one

[1] This is not what is reported in the paper (see section 4.4.1)

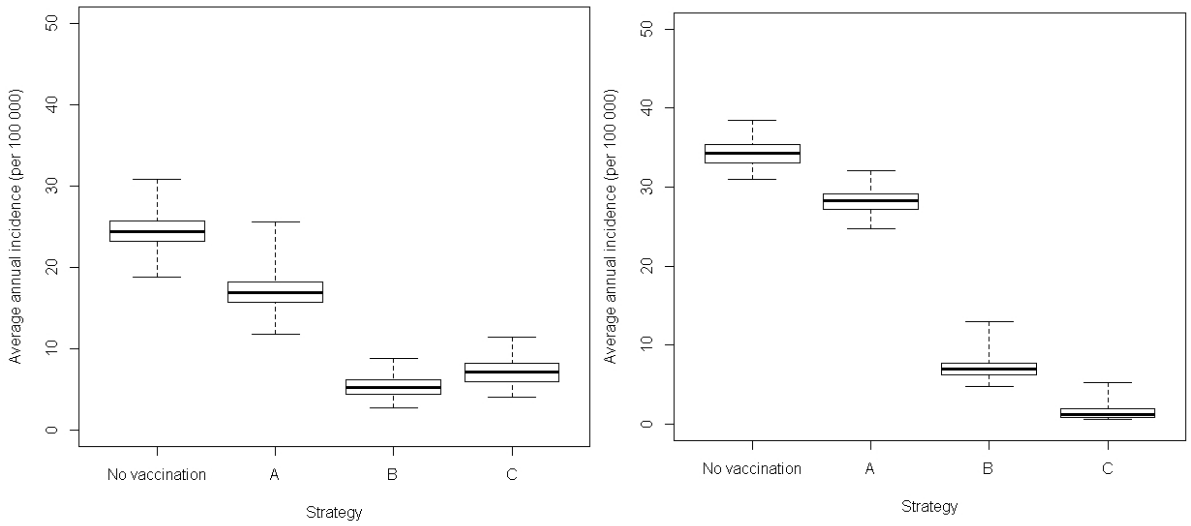
day. Further details on the model structure and initial conditions used can be found in Chapter 3.

4.2.3 Vaccination strategies

The two models explored the relative effectiveness of a range of different vaccination strategies and compared them to a scenario without any vaccination and with only the initial mass campaign of 1-29 year olds. The strategies that both models considered were routine immunisation at 9 months of age as well as periodic mass campaigns of 1-4 year olds every 5 years.

4.2.4 Model predictions

In the base case scenario, both models suggest that introduction of MenAfriVac in the Expanded Programme on Immunisation (EPI) and follow-up mass campaigns would reduce the incidence of invasive disease compared to no long-term vaccination.



(a) Karachaliou et al.

(b) Tartof et al.

Fig. 4.2 Boxplot to show the median, interquartile range and full range of the predicted annual incidence for different immunisation strategies. (A) Initial mass campaign only, (B) Routine EPI at 9 months, (C) Periodic campaigns of 1-4 year olds every 5 years. Left panel: Results from Karachaliou *et al.* model. Right panel: Figure produced using Tartof *et al.* model and parameter values as in the published paper.

The results produced by the two models can be seen in Fig 4.2. The Tartof model [84] suggests that periodic campaigns of 1-4 year olds would prevent the most cases of all strategies considered. They report a mean of 1.6 cases per 100,000 per year if periodic campaigns take place every 5 years, compared to a mean rate of 7.3/100,000 per year if MenAfriVac is introduced into EPI 5 years after the initial mass campaign. On the contrary, our model suggests that although there was considerable overlap in the distribution of results, routine EPI immunisation at 9 months resulted in lower mean annual incidence than periodic mass campaigns of 1-4 year olds. Note here that the strategy D from Chapter 3 is not shown here as this strategy was not explored by Tartof *et al.* and thus, there could be no direct comparison.

4.3 Similarities and differences

4.3.1 Similarities

Both models are age-structured, stochastic models. An episode of colonisation or disease offers complete protection against future colonisation for a certain period of time.

4.3.2 Differences

The ageing process is different in the two models. Tartof *et al.* use discrete ageing by moving individuals from one age group to the next every month, whereas I implemented continuous ageing between age groups.

The duration of vaccine protection in the two models are not directly comparable. My model assumed an average duration of vaccine protection of 10 years regardless of the age at vaccination. In the other model, a dose of the vaccine is equivalent to natural infection, therefore, when individuals are vaccinated in ages older than 10 years, the protection is lifelong. Vaccination of children between 2 and 10 years of age also leads to an average of 25 years duration of protection. The exact parameter values can be found in Table 1 of their paper.

A summary of the differences between the two models can be seen in Table 4.1.

4.4 Comparison process

To begin the comparison process, it was more convenient for me to have two working models that were coded in the same programming language so that they can easily be

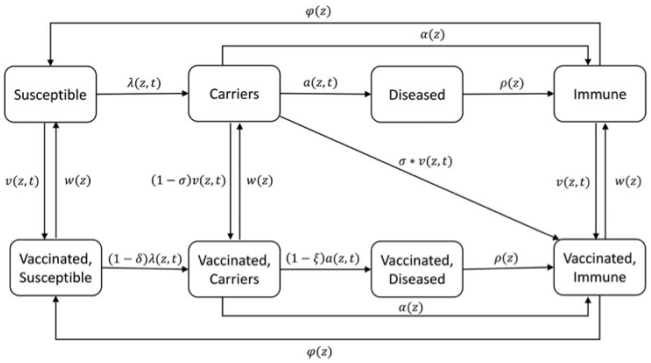
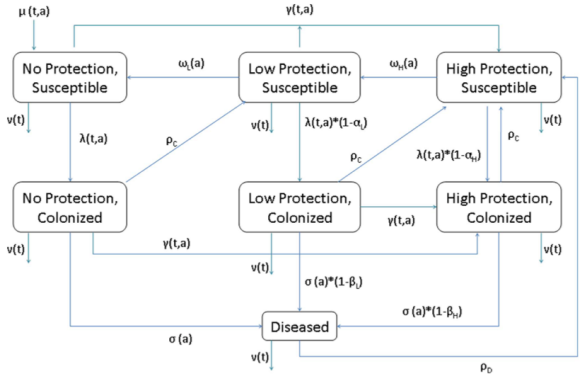
Characteristic	**Karachaliou** ***et al.***	**Tartof** ***et al.***
Structure		
Ageing	Continuous (19 age groups)	Discrete (361 age groups)
System	Differential equations	Difference equations
Vaccine duration	10 years	Age dependent (20 - 25 years)
Stochastic term	Annually (0.8 - 1.2)	Weekly (0.25 - 1.75)
Time Step	1 day	1 calendar week
Language	R	SAS

Table 4.1 Summary of the differences between the two models.

modified. Since the Tartof model was coded in SAS, I decided to recode their paper into R, which is a free software. Another reason for choosing to use the same programming language to implement the two models was to reduce sources of variation, such as using different solvers. Further, independent implementation of a model can identify any possible coding errors.

My initial aim was to replicate the results presented in the paper so that I am confident that the code is the same as the one used by the other team. I sourced all the information and the parameter values from the paper. My initial attempt to reproduce the results was unsuccessful. The average annual incidence my code was estimating was far lower than the average yearly incidence in the paper.

4.4.1 Errors in code/paper

After communicating with the authors, I discovered that two of the key parameters -the transmission rate and the rate at which carriers develop invasive disease- were not scaled appropriately when reported in the paper. The rates provided in the article are weekly rates and not annual as stated. Using the correct values, however, did not improve my model predictions. I was still unable to reproduce the results in the initial published study.

My next step was to request for the source code from the authors. I then discovered some more discrepancies between the information in the paper and the code that was actually used to produce the results.

- In the paper, the stochastic term is described as a random number between 0 and 0.75. The stochastic term actually used was drawn from a U-shaped distribution with range (0.25-1.75).
- The duration of disease was assumed to be 10 days, compared to 7 days listed in the paper.
- The rate of waning of immunity depends on age, and it is lower for individuals older than 2 years of age, compared to 3 years listed in the paper.

Changing the duration of disease and the age-specific rate of waning did not have a great effect on the dynamics, but the imprecise stochastic term was influential.

4.4.2 Implementation issues

The main issue that prevented me from correctly reproducing the results in Tartof *et al.* was the way periodic campaigns were implemented. The periodic campaigns targeting 1-4 year-olds every five years were implemented monthly over the course of a whole year instead of occurring as a discrete event at one point in time. This implementation was wrong as it does not correspond to reality and resulted in the vaccination of an additional age cohort. The initial mass campaign in 2010 was completed in only ten days [7]. It would be reasonable to assume that the periodic campaigns would take place in a similar way and not once a month over a period of one year.

Another difference between the papers is the period for which the average annual incidence is calculated. Tartof *et al.* included the year 2010 in their calculations even though initial mass campaign took place in December 2010. I estimated the average annual incidence for the first 40 years after the initial campaigns.

Lastly, I noticed that although dry season runs from December through May (6 months), the rate at which carriers develop disease takes a higher value during seven months of the year. This was ambiguous in the paper and it is not clear whether it was intentional or another coding error.

A summary of all the implementation issues is given in Table 4.2. The results presented in the Tartof model are therefore not consistent with the model shown in the paper. This finding led to a correction to the original paper in 2017 [105].

Reported in paper	**What was actually done**
Annual rates	Weekly rates
Stochastic term (0 - 0.75)	Stochastic term (0.25 - 1.75)
Duration of disease 7 days	Duration of disease 10 days
Age group 3 - 10 years of age	Age group 2 - 10 years of age
High invasion rate period 6 months	High invasion rate period 7 months

Table 4.2 Summary of errors in reporting in Tartof *et al.*.

After taking into consideration of all the issues shown in Table 4.2, I was finally able to reproduce the results in the paper (Figure 4.3).

All this work provided a corrected Tartof model to use for the model comparison. Altering the implementation of the periodic campaigns, as shown in Figure 4.4, if campaigns of 1 to 4 year olds take place in one week only every five years, as expected, the estimated average annual incidence is higher.

Comparing again the benefits of routine immunisation at nine months and periodic campaigns targeting children 1 to 4 years of age, it is shown in Figure 4.5 that there is considerable overlap in the distribution of results. However, if we simply look at the median values across 100 model runs, the argument that periodic campaigns are more effective than routine EPI still holds.

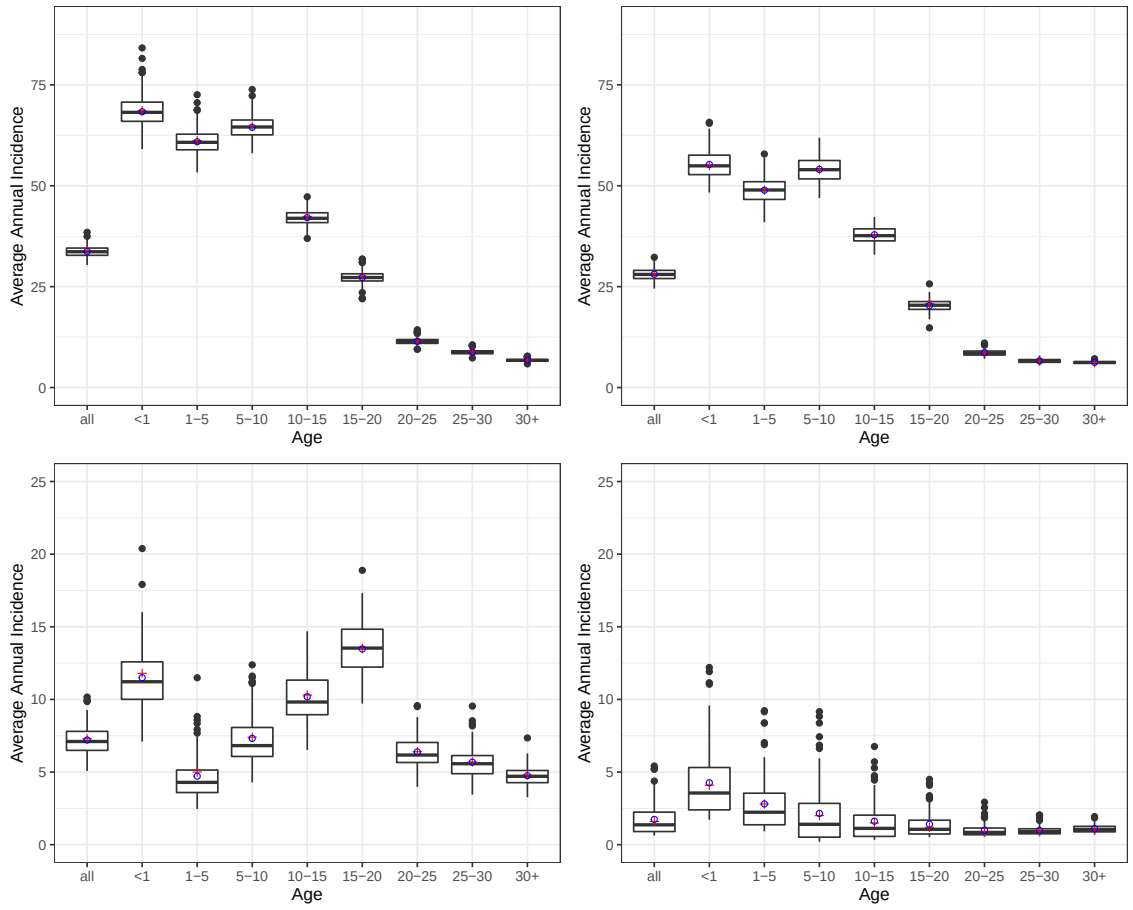


Fig. 4.3 Boxplot to show the median, interquartile range and full range of the average annual incidence from 100 simulation runs with discrete ageing based on my implementation of Tartof model in R. Red marks indicate the mean values which can be found in Table 2 of their paper and blue circles represented the mean from the simulations. Strategies from top to bottom and left to right: No vaccination, A, B and C.

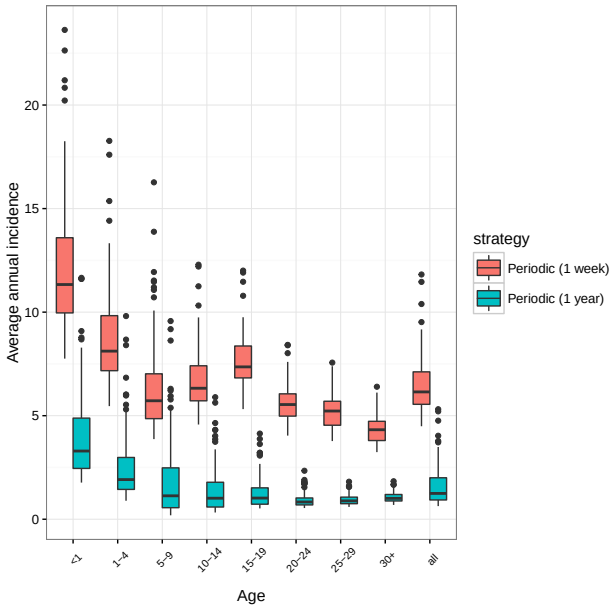


Fig. 4.4 Boxplot to show the median, interquartile range and full range of the average annual incidence from 100 model runs of the Tartof *et al.* model for periodic campaigns (strategy C) over a course of a year every 5 years compared to periodic campaigns taking place in one week every 5 years.

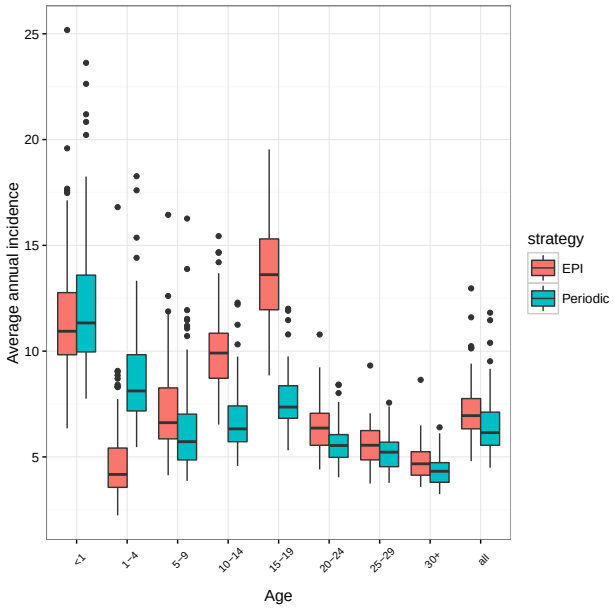


Fig. 4.5 Boxplot to show the median, interquartile range and full range of the average annual incidence from 100 model runs for periodic campaigns every 5 years (strategy C) compared to EPI at 9 months (strategy B).

4.4.3 Continuous model

To aid the model comparison, I decided to re-implement the Tartof model using differential equations and continuous ageing. Using the same simulation/integration routine allows me to explore differences in structure only.

I divided the population into 33 age groups: 0 to <6 months, 6 to <9 months, 9 to <12 months, and one year age groups to age 30. Similarly to the discrete model, individuals who are 30 years and older are treated as one homogeneous age group. The parameters were set to exactly the same values as in the discrete model. The time step was one day. The methodology to derive the age-structured model is described in Chapter 3 and more details can be found in Appendix A.

The difference equations were re-written as a set of differential equations to implement continuous ageing between age groups:

$$
\begin{aligned}
&\text{for } j = 2, \ldots, 33 \\
\frac{dNS_1}{dt} &= (K_1 + d_1 + q)P_1 - (K_1 + d_1 + q)NS_1 + w_{L_1}LS_1 - \lambda_1 NS_1 - f_o NS_1 \\
\frac{dNS_j}{dt} &= K_{j-1}NS_{j-1} - (K_j + d_j + q)NS_j + w_{L_j}LS_j - \lambda_j NS_j - f_o NS_j \\
\frac{dLS_1}{dt} &= \rho_C NC_1 - (K_1 + d_1 + q)LS_1 - w_{L_1}LS_1 - \lambda_1(1 - a_L)LS_1 + w_{H_1}HS_1 - f_o LS_1 \\
\frac{dLS_j}{dt} &= K_{j-1}LS_{j-1} + \rho_c NC_j - (K_j + d_j + q)LS_j - w_{L_j}LS_j - \lambda_j(1 - a_L)LS_j + w_{H_j}HS_j - f_o LS_j \\
\frac{dHS_1}{dt} &= \rho_C LC_1 + \rho_C HC_1 + \rho_D D_1 - \lambda_1(1 - a_H)HS_1 - w_{H_1}HS_1 - (K_1 + d_1 + q)HS_1 - f_o HS_1 \\
\frac{dHS_j}{dt} &= K_{j-1}HS_{j-1} + \rho_C LC_j + \rho_C HC_j + \rho_D D_j - \lambda_j(1 - a_H)HS_j - w_{H_j}HS_j \\
&\quad - (K_j + d_j + q)HS_j - f_o HS_j \\
\frac{dNC_1}{dt} &= \lambda_1 NS_1 - \rho_C NC_1 - \sigma_1 NC_1 - (K_1 + d_1 + q)NC_1 + f_o NS_1 \\
\frac{dNC_j}{dt} &= K_{j-1}NC_{j-1} + \lambda_j NS_j - \rho_C NC_j - \sigma_j NC_j - (K_j + d_j + q)NC_j + f_o NS_j \\
\frac{dLC_1}{dt} &= \lambda_1(1 - a_L)LS_1 - \rho_C LC_1 - \sigma_1(1 - \beta_L)LC_1 - (K_1 + d_1 + q)LC_1 + f_o LS_1 \\
\frac{dLC_j}{dt} &= K_{j-1}LC_{j-1} + \lambda_j(1 - a_L)LS_j - \rho_C LC_j - \sigma_j(1 - \beta_L)LC_j - (K_j + d_j + q)LC_j + f_o LS_j \\
\frac{dHC_1}{dt} &= \lambda_1(1 - a_H)HS_1 - \rho_C HC_1 - \sigma_1(1 - \beta_H)HC_1 - (K_1 + d_1 + q)HC_1 + f_o HS_1 \\
\frac{dHC_j}{dt} &= K_{j-1}HC_{j-1} + \lambda_j(1 - a_H)HS_j - \rho_C HC_j - \sigma_j(1 - \beta_H)HC_j - (K_j + d_j + q)HC_j + f_o HS_j
\end{aligned}
$$

$$\frac{dD_1}{dt} = \sigma_1(1-\beta_L)LC_1 + \sigma_1(1-\beta_H)HC_1 + \sigma_1 NC_1 - \rho_D D_1 - (K_1 + d_1 + q)D_1$$
$$\frac{dD_j}{dt} = K_{j-1}D_{j-1} + \sigma_j(1-\beta_L)LC_j + \sigma_j(1-\beta_H)HC_j + \sigma_j NC_j - \rho_D D_j - (K_j + d_j + q)D_j$$

Parameter name	**Description**	**Value**
K	Rate at which people move between age groups	0-3.98/year
d	Mortality rate	0.01302-0.02/year
q	Country's growth rate	0.0308/year
λ	Force of infection	-
f_o	External force of infection	0.0005/year
w_L	Waning of low protection to none	0.04-0.4/year
w_H	Waning of high protection to low	0.025-0.877/year
a_L	Immunity of low protection against colonisation	0.25
a_H	Immunity of high protection against colonisation	0.75
σ	Rate at which carriers develop disease	0.089-0.098/year
β_L	Immunity of low protection against disease	0.9
β_H	Immunity of high protection against disease	1
ρ_C	Rate of recovery from colonisation	12.175/year
ρ_D	Rate of recovery from disease	36.5249/year

Table 4.3 Description and values of parameters in Tartof model with continuous ageing. A range is given for age-dependent values.

A list of parameter names and their description is given in Table 4.3. The mortality rate is assumed to be the same for the first 32 age groups and is set to 0.02/year for the last age group to ensure that all individuals die by the age of 80 years. For each simulation, I ran the model for a 20-year burn-in period before implementing the initial mass vaccination campaign. In the absence of vaccination as well as if only the initial large-scale vaccination campaign takes place, as shown in the top panel in Figure 4.6, the differential equations and the difference equations models produce very similar

results across all ages. Continuous and discrete ageing yield very similar results when MenAfriVac is introduced into EPI at nine months of age. The estimated average annual incidence though, as shown in bottom panel in Figure 4.6, is higher in the continuous model.

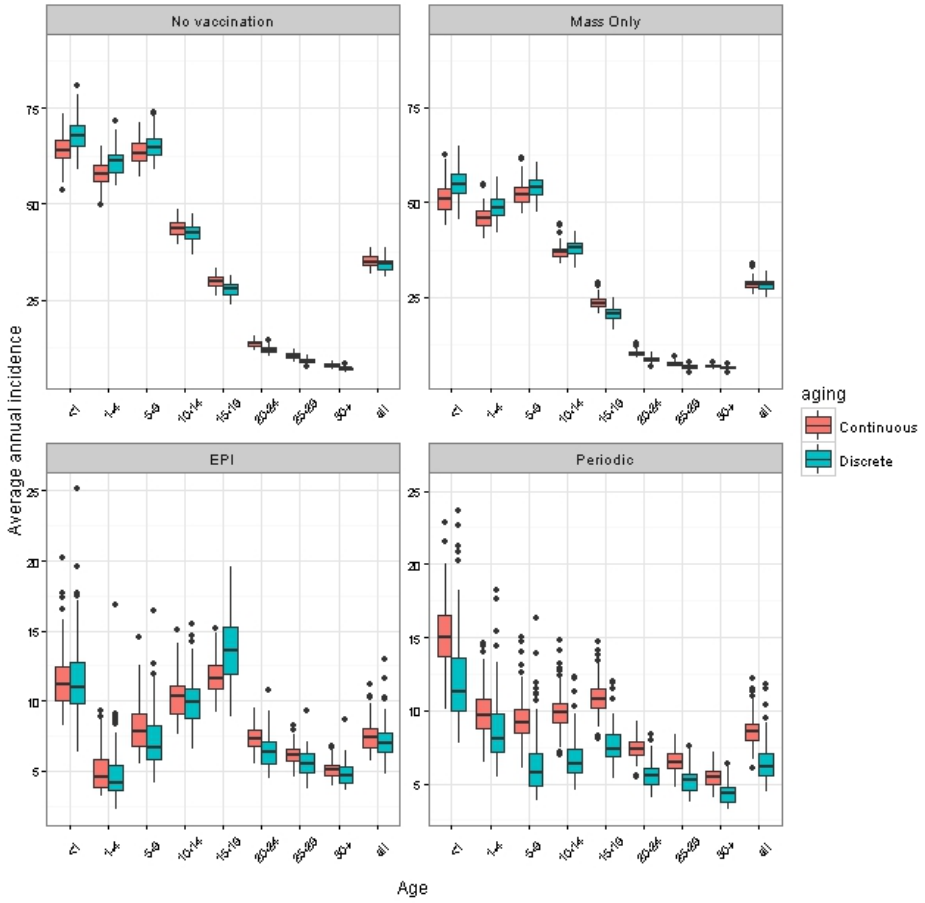


Fig. 4.6 Boxplot to show the median, interquartile range and full range of the average annual incidence under different ageing processes and immunisation strategies. From 100 simulation runs for the time period 2010-2050.

Comparing again EPI and periodic campaigns for the continuous model, as shown in Figure 4.7, the model suggests that routine EPI at 9 months is more effective than periodic campaigns. This agrees with the results from my model presented in Table 3.5. The main difference in the results of the two models which triggered this comparison study initially was that Tartof *et al.* suggested that routine EPI was less effective than periodic campaigns. From this work, I found that the ageing process seems to be influential in predicting the relative impact of the two vaccination strategies compared.

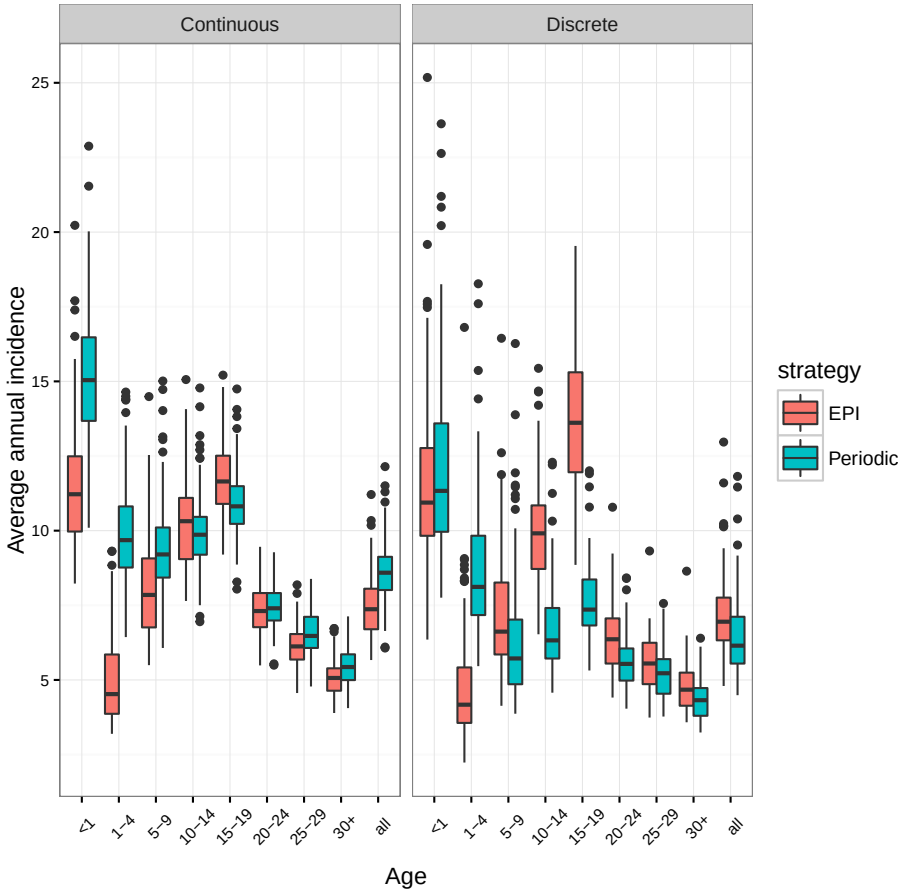


Fig. 4.7 Boxplot to show the median, interquartile range and full range of the average annual incidence for the routine EPI and periodic campaigns for continuous and discrete ageing processes.

4.4.4 From discrete to continuous model

Each choice between difference and differential equations has its advantages and disadvantages in the modelling process. Continuous models are obtained using the same principles as corresponding discrete models. An important question is whether discrete and continuous models are consistent in the sense that they give the same solutions or solutions with the same qualitative features [92]. Since time discretisation can cause problems when numerically solving differential equations, I decided to examine how a different step size would affect the results of the discrete model. To explore that, I removed the stochastic term and reduced the time step from one calendar week to one day. The results are shown in Table 4.4. In the absence of vaccination and when only the mass vaccination campaign takes place, the model seems to have 'converged', since the

results with a step size of one week are similar to those based on a one-day step size. The fact that the model predicts higher incidence for a smaller step size when considering long-term immunisation strategies suggests that the time step of one calendar week may not be sufficiently small to actually predict the epidemic curve.

Age	No vax (week)	No vax (day)	Mass (week)	Mass (day)	EPI (week)	EPI (day)	Periodic (week)	Periodic (day)
<1	74.44	77.00	60.17	62.25	12.49	13.09	12.59	13.68
1-4	66.47	68.22	53.32	54.83	5.06	5.18	8.94	9.79
5-9	66.04	65.94	56.12	56.24	7.71	7.88	6.47	6.80
10-14	41.61	41.20	37.30	36.69	11.24	11.81	6.90	7.36
15-19	25.97	25.37	19.69	19.32	14.59	14.83	8.09	8.66
20-24	10.34	9.96	7.89	7.62	6.21	6.36	5.81	6.12
25-29	8.58	8.28	6.48	6.31	5.75	5.64	5.34	5.56
30+	6.73	6.58	6.30	6.20	4.97	5.14	4.50	4.71
All	34.99	35.16	29.15	29.33	7.66	7.89	6.67	7.11

Table 4.4 Numerical solution of discrete Tartof model using a time step of 1 calendar week and 1 day.

Just changing from discrete to continuous time, leaving the model structure and parameters unchanged can yield a different Reproduction number (R_0). I believe that this is the reason for the discrepancy between the results of the difference and differential equations systems but have not pursued further technical analysis of this issue.

4.5 Discussion

Two models have been published to date looking at the effect of a number of immunisation strategies with MenAfriVac in the African meningitis belt. The two models exhibit several differences, including the model structure, and they make different predictions regarding the relative benefits of the immunisation strategies they considered. I decided to start a model comparison process in an effort to identify which features of the models are responsible for the observed differences in their predictions.

Initially, I believed that the different assumption for the duration of immunity after vaccination was the driver of the observed differences in model predictions. However,

in the process, I discovered that Tartof *et al.* had implemented the periodic campaigns differently. The different implementation was the reason their model predicted that periodic campaigns were more effective than incorporating MenAfriVac into the routine EPI schedule. When I altered the way follow-up campaigns were implemented, although periodic campaigns resulted in lower average annual incidence than EPI, there was considerable overlap in the distribution of results. This finding was communicated back to the authors and that resulted in them publishing a correction to the original paper [105].

When I implemented the same model with continuous ageing, the model predicted that EPI was superior to periodic campaigns. That is, the results from my model and the model developed by Tartof *et al.* followed the same pattern. This indicated that the key feature responsible for the observed differences in the two models' predictions is the choice of the ageing process. When numerically solving difference and differential equations, there is always an error in the approximations. An additional error is introduced when converting a set of difference equations to a set of differential equations. It is challenging to quantify these accumulated errors.

This model comparison exercise has been useful in allowing me to examine differences in both the reported and code based predictions of NmA vaccine impact. Some issues can be easily resolved, such as the implementation of periodic mass campaigns. Other issues, such as decisions on ageing processes, are more challenging, but nevertheless could still be influencing model predictions. When measuring vaccine impact, guidelines from WHO (currently being updated) and Gavi (VIMC) could be helpful in this regard to ensure consistency.

Chapter 5

Vaccine Impact Modelling Consortium

5.1 Introduction

The Vaccine Impact Modelling Consortium (VIMC) [106] was established in 2016 for a period of five years. The aim of the Consortium is to coordinate the work of several research groups modelling the impact of vaccination programmes that are supported by Gavi [107]. The reason behind the coordination of all modelling activities into a Consortium is to harmonise the assumptions made by the different modelling groups working around the globe to ensure the best possible quality of the estimates produced by the teams. A secretariat based at Imperial College London coordinates the work being carried out by the Consortium members. It consists of a management group as well as administrative, scientific and technical teams.

The Consortium will work on aggregating estimates from a portfolio of ten vaccine-preventable diseases and further advancing the research agenda in the field of vaccine impact modelling. Gavi, the Vaccine Alliance and the Bill & Melinda Gates Foundation are funding the Consortium and plan to use the data generated by its members to monitor their progress towards the Decade of Vaccines targets and inform potential future investments and vaccine scale-up opportunities.

I will outline the changes necessary to fit within VIMC guidelines and the new results and outputs that were obtained.

5.2 Montagu

Working with all the participating modelling groups, the secretariat has developed a web-based delivery platform, called Montagu. All the members of the VIMC can interact with Montagu through different portals. Modellers can have easy access to the latest demographic and coverage data to ensure consistency between the groups, while funders can quickly access the estimates and browse through several reports generated by the secretariat.

Each time an input parameter, such as the coverage data, is updated, Montagu starts a new 'touchstone' which enables strict version control. This feature provides an easy way to trace back the input data that were fed into the models generating specific burden estimate sets.

Through the modellers' contribution portal, the modelling groups, apart from coverage data and life tables, can also download burden estimate templates which guide them to produce the right type of output. The completed template with the estimates can be uploaded into the platform at the end of the modelling round.

5.3 Description of deliverables

There are rounds of modelling taking place every odd-numbered year. The most recent modelling round took place in December 2017. All modellers were asked to provide estimates of disease burden in terms of number of cases, deaths, and Disability Adjusted Life Years (DALYs) stratified by country, age and year for the 96 Gavi-supported and Decade of Vaccines countries. The burden should be reported by calendar year, and stratified by age into annual age cohorts. Estimates for a number of vaccination coverage scenarios, including various routine and campaign strategies were requested, shown in Table 5.1.

More specifically, for NmA, the disease-specific ranges to be explored are shown in Table 5.2. MenAfriVac is being administrated in the 26 countries of the African meningitis belt. The time horizon is set to be from the introduction of the vaccine in 2010 until 2100. Not all countries introduce MenAfriVac in the same year though. All introductory campaigns take place during the period 2010-2020 as illustrated in Figure 5.1. In Figure 5.1 we can see that the introductory campaign in 8 countries, namely Mali, Niger, Cameroon, Chad, Nigeria, Senegal, Sudan and Ethiopia, took place across more than one year. This is due to the campaign being completed in phases targeting

Scenario	Schedule
No vaccination	-
Campaign	1 dose for 1-29 year olds in introductory campaigns 1 dose for over 1 year olds in catch-up campaigns
Campaign & routine	1 dose for 1-29 year olds in introductory campaigns 1 dose for over 1 year olds in catch-up campaigns 1 dose in routine programme given at 12 months of age

Table 5.1 Immunisation strategies requested from Gavi to provide estimates for during the modelling round in 2017.

different parts of the country in each phase. Although Gavi require impact estimates to 2030, the time horizon is extended to 2100 in order to capture the lifetime burden of any vaccinated cohorts, allowing for generation of burden by year of vaccination estimates. Due to the stochastic nature of the model, 200 model runs were required by the VIMC secretariat. The full amount of age and year stratified data generated from the stochastic runs for all the countries and across all three scenarios exceeds 140 million rows.

Disease	Number of countrives targeted	Age range	Time horizon	Vaccination strategy
MenA	26	0-99	2010-2100	no vaccination, campaign only, campaign and routine

Table 5.2 MenA-specific ranges and scenarios to be considered for the generation of vaccine impact estimates for round 2017.

5.4 Incidence by country

In order to meet the deliverables above, I needed to modify the model from Chapter 3. I recognise that there is diversity in the incidence of meningitis in the countries of the African meningitis belt. For some countries there are also rather poor data, e.g only 9 were considered to have consistent high quality data in a recent epidemiological assessment of the impact of MenAfriVac to date [108]. Rather than parameterise 26 different models, I felt it was more appropriate to classify countries into categories, based on the incidence levels, which would define the transmission dynamic parameters of the model.

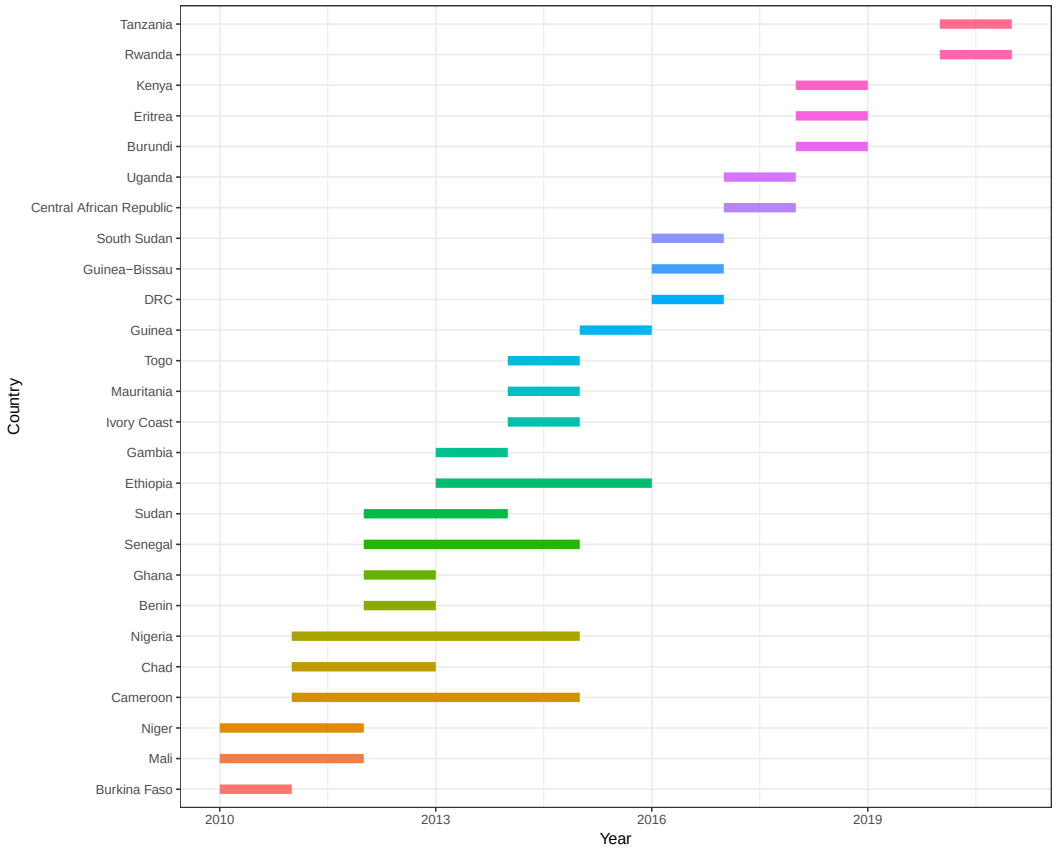


Fig. 5.1 Year of MenAfriVac introduction in the 26 countries of the African meningitis belt.

Not all countries lie entirely in the African meningitis belt. The belt consists of seven countries in their entirety and parts of other countries, where only a fraction of their population is considered to be at high risk of meningococcal meningitis according to WHO. The proportion of the population assumed to be at risk in each country is illustrated in Figure 5.2 and is as follows:

- 7 countries (100% population at risk)
  - Burkina Faso, Chad, Ethiopia, Gambia, Mali, Niger, Sudan
- Nigeria (70% population at risk)
- South Sudan (50% population at risk)
- 12 countries (20% population at risk)

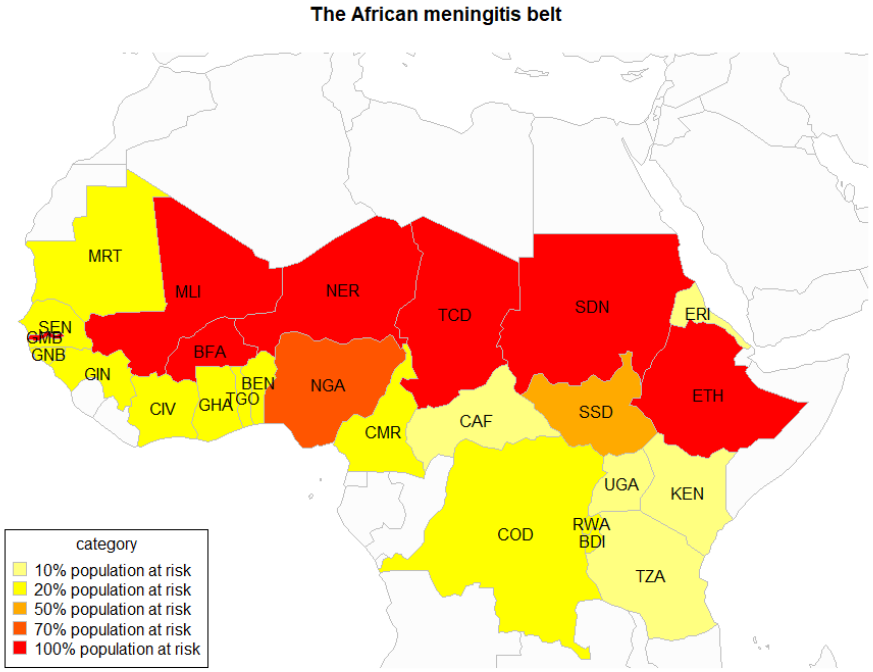


Fig. 5.2 Map showing the proportion of people considered to be at risk of meningococcal meningitis in the countries of the African meningitis belt. Three letter code is used for the names of countries. BDI - Burundi, BEN - Benin, BFA - Burkina Faso, CAF - Central African Republic, CIV - Cote d'Ivoire, CMR - Cameroon, COD - Democratic Republic of the Congo, ERI - Eritrea, ETH - Ethiopia, GHA - Ghana, GIN - Guinea, GMB - Gambia, GNB - Guinea-Bissau, KEN - Kenya, MLI - Mali, MRT - Mauritania, NER - Niger, NGA - Nigeria, RWA - Rwanda, SDN - Sudan, SEN - Senegal, SSD - South Sudan, TCD - Chad, TGO - Togo, TZA - Tanzania, UGA - Uganda.

  - Benin, Cameroon, Democratic Republic of the Congo, Ghana, Guinea, Guinea-Bissau, Rwanda, Mauritania, Senegal, Burundi, Cote d'Ivoire, Togo

- 5 countries (10% population at risk)

  - Central African Republic, Eritrea, Kenya, Tanzania, Uganda

In the MenA Investment Case written in 2008 (Marie-Pierre Preziosi, personal communication, October 20, 2015), the 26 countries were classified as follows:

- Core countries (N=7)

  - Burkina Faso, Ethiopia, Mali, Niger, Sudan, 26 northern states of Nigeria

- Bordering countries with hyperendemic zones (N=12)
  - Benin, Cameroon, Central African Republic, Cote d'Ivoire, Democratic Republic of the Congo, The Gambia, Ghana, Kenya, Togo, Senegal, Uganda and the remaining states of Nigeria

- Other at-risk countries without hyperendemic zones (N=7)
  - Burundi, Eritrea, Guinea, Guinea-Bissau, Mauritania, Rwanda and Tanzania

I examined the available historic reports [31] and more recent surveillance data [12] to investigate whether the categories defined in the investment case were suitable for the modelling purposes, or whether an updated classification was more appropriate.

Based on these data, summarised in Table 5.3, it is clear that Burkina Faso and Niger have the highest incidence, with frequent large outbreaks. The incidence during an outbreak in these countries exceeds 400 cases per 100,000 population. For other countries included in the 'core' category above, such as Mali and Chad, these data suggest that the average annual incidence is substantially lower than for Burkina Faso and Niger.

Some countries have very little reported data making it difficult to categorise them solely based on the incidence. Therefore, I decided to classify them using additional information on their geographical position and year of MenAfriVac introduction, into High-Medium-Low incidence categories. Countries that are located near the two high incidence nations and which introduced MenAfriVac before the year 2015, were assigned in the medium incidence category, with all the rest assigned in the low incidence category.

Looking at the reported annual incidence of the countries for the periods 1980-1999 and 2005-2010, in Table 5.3, the countries with a median annual incidence of more than 5 cases per 100,000 population and frequent large outbreaks are assigned to the 'Medium' category. The 'Low' category consists of countries with lower reported annual rates of disease as well as smaller and less frequent epidemics. This categorisation was discussed and agreed with WHO colleagues in July 2017.

Country	Lingani *et al.* 2005-2010 Mean (range)	Lingani *et al.* 2005-2010 Median	Molesworth *et al.* 1980-1999 Median (range)	Category
Benin	4.28 (2.7-11.6)	4.12	11 (6-57)	Low
Burkina Faso	83.11 (13.1-188.4)	56.88	48 (9-438)	High
Chad	14.18 (1.2-48.4)	13.27	18 (0-150)	Medium
Cote d'Ivoire	3.14 (0.5-5.8)	3.35	1 (0-6)	Low
Ghana	2.31 (1.1-4.6)	1.98	6 (0-108)	Medium
Mali	5.78 (1.6-10.8)	5.31	15 (3-119)	Medium
Niger	29.73 (1.6-85.8)	21.37	53 (16-490)	High
Nigeria	8.34 (0.4-36.1)	3.56	5 (1-98)	Medium
Togo	8.03 (2.5-12.2)	7.13	8 (1-77)	Medium
Mauritania	-	-	4 (0-14)	Low
Cameroon	-	-	17 (1-224)	Medium
Central African Republic	-	-	16 (0-48)	Low
Eritrea	-	-	0 (0-0)	Low
Ethiopia	-	-	1 (0-104)	Medium
Gambia	-	-	7 (4-165)	Medium
Guinea	-	-	3 (0-17)	Low
Guinea-Bissau	-	-	2 (0-133)	Low
Senegal	-	-	3 (0-53)	Low
Sudan	-	-	3 (1-140)	Medium
Democratic Republic of the Congo	-	-	2 (0-6)	Low
Burundi	-	-	1 (0-49)	Low
Kenya	-	-	4 (0-15)	Low
Rwanda	-	-	3 (0-28)	Low
Uganda	-	-	5 (0-18)	Low
Tanzania	-	-	2 (0-19)	Low

Table 5.3 The average and median incidence for countries of the African meningitis belt taken from [31, 12]. All numbers are cases per 100,000 population per annum.

5.5 Methods

In order to meet the requirements set by the VIMC, some changes needed to be made to the model developed and presented in Chapter 3. I changed the model from having broad age groups into annual age cohorts. Originally, it was assumed that the age distribution was stationary, that is that the proportion of people in each age group did not change over time. To achieve that, I had assumed that the country's annual growth rate was constant each year. For this modelling round I used country- and year-specific birth rates to parameterise the models. All vaccine-associated parameters are the same as in Chapter 3. Different values for the contact parameters are used to run the simulations for the countries in the three incidence categories. These values are shown in Table 5.4 and were chosen so that model simulations resulted in an average of 45-50 cases per 100,000 people in the 'High' category countries, 20-25 cases per 100,000 population in the 'Medium' category countries and no more than 5 cases per 100,000 population in countries in the 'Low' category in the absence of any vaccination.

Parameter	**Category**	**Value**
Transmission rate	High	16.8
	Medium	9.45
	Low	7.35

Table 5.4 Values for the transmission rate parameters used in the model simulations.

5.5.1 Initial conditions

I divided the population into a hundred discrete age groups based on their age. That is, the first age group consists of individuals who were just born plus all individuals who have not had their first birthday yet. The second age group consists of individuals who are between one and two years of age and so on. All individuals within a particular age group are assumed to be equal with respect to their mortality rates. A newborn enters the first age class upon birth and progresses to the next age class at a rate κ.

Initially, I assumed that the growth rate of each country in the year 2010 is equal to zero. The ageing process in a population that has zero growth rate is described by the following equations:

$$BN - \kappa N_1 - \mu_1 N_1 = 0; \qquad i = 1$$

$$\kappa N_{i-1} - \kappa N_i - \mu_i N_i = 0; \qquad 2 \leq i \leq L-1$$
$$\kappa N_{L-1} - \mu_L N_L = 0; \qquad i = L$$

where N is the total population, N_j is the population size in age group j, μ is the age-specific death rate, κ is the rate of ageing and B is the birth rate. The model was run using a daily time step and therefore κ is equal to 1/365. Rearranging, we can calculate the age-specific mortality rates for the year 2010 using values for the population size and birth rate taken from United Nations Population Division (UNPOP).

$$\mu_1 = \frac{BN}{N_1} - \kappa; \qquad i = 1$$
$$\mu_i = \kappa(\frac{N_{i-1}}{N_i} - 1); \qquad 2 \leq i \leq L-1$$
$$\mu_L = \kappa\frac{N_{L-1}}{N_L}; \qquad i = L$$

I set 1% of the population in the carrier state and used the above death rates in order to run the model for a burn-in period of 50 years while the population remained constant. The model was subsequently run for the time period 2010-2100 with initial conditions the state of the system at the end of the 50-year burn-in period and the year- and age-specific birth and mortality rates taken from UNPOP.

5.5.2 Vaccination coverage

Projections of demand and vaccination coverage for the 2010-2100 time horizon were provided by Gavi. For routine immunisation there was a 1% annual increment in coverage with a 90% cap. The lowest bound of coverage was 5.9% in Togo during the first year of the country's introduction of MenAfriVac into the routine vaccination programme. Four countries with very low observed incidence of meningococcal meningitis, namely Burundi, Kenya, Rwanda and Tanzania, are not planning to introduce MenAfriVac into routine immunisation.

Not all countries are assumed to be at high risk of meningitis as I discussed in section 5.4. To calculate the coverage for the introductory mass campaign, I started by dividing the number of individuals targeted by the total number of people in the targeted age groups in the year of vaccination. This gave me the proportion of the population targeted

for vaccination. I then multiplied that proportion with the reported coverage, to get the final coverage which I used in the model.

Most countries also plan to have a catch-up campaign in the same year as the introduction of MenAfriVac into their routine immunisation schedule, targeting children who were either born after the initial campaigns or were too young to be immunised then. The 100% coverage rate provided by Gavi for this mini vaccination campaign was sub-national immunisation coverage. That is, only children from the proportion of the country considered to be at risk (see Section 5.4) are eligible for vaccination. For countries that lie entirely in the African meningitis belt, such as Burkina Faso and Niger, this means 100% coverage, while for countries with 20% or 10% of their population considered to be at risk, the coverage is 20% and 10% respectively. Eritrea and Central African Republic completed the mass campaign and started the routine immunisation of infants in the same year and therefore there is no catch-up campaign

Even though campaigns may be taking place at a sub-national level, after communication with WHO, it was determined that routine immunisation should be modelled so that it is introduced nationwide in all countries.

Table 5.5 shows the vaccination schedule for all the 26 African nations. Gavi coverage estimates for the initial mass campaign might differ from the proportion of population at risk shown in Figure 5.2.

5.5.3 Calculation of DALYS

The disability-adjusted life year (DALY) is a measure of the burden of disease [109]. It is commonly used by researchers who wish to compare populations and diseases as it quantifies the burden of disease from mortality and morbidity. One DALY can be considered as the loss of one year of full health.

DALYs are calculated as the sum of two components: the Years of Life Lost (YLL) and Years Lost due to Disability (YLD).

$$DALY = YLL + YLD \tag{5.1}$$

The YLL represents the years lost due to early death caused by a disease. It is calculated by multiplying the number of deaths by the life expectancy at the age of death, as follows:

$$YLL = \sum_{a=1}^{100} D_a L_a \tag{5.2}$$

Country	Year of mass campaign	Target age for mass campaign	Proportion targeted for mass campaign	Year of routine and/or catch-up	Target age for catch-up	Coverage for catch-up
Benin (BEN)	2012	1-29	39.6%	2019	1-7	20%
Burkina Faso (BFA)	2010	1-29	100%	2016	1-6	100%
Burundi (BDI)	2018	1-29	17.5%	-	-	-
Cameroon (CMR)	2011-2014	1-29	43%	2018	1-8	20%
CAR (CAF)	2017	1-29	100%	2017	-	-
Chad (TCD)	2011-2012	1-29	93%	2017	1-6	100%
DRC (COD)	2016	1-29	33.7%	2019	1-4	20%
Cote d'Ivoire (CIV)	2014	1-29	28.3%	2018	1-4	20%
Eritrea (ERI)	2018	1-29	11%	2018	-	-
Ethiopia (ETH)	2013-2015	1-29	95.5%	2018	1-6	100%
Gambia (GMB)	2013	1-29	91.1%	2017	1-5	100%
Ghana (GHA)	2012	1-29	18.3%	2016	1-5	19.6%
Guinea (GIN)	2015	1-29	30.2%	2019	1-4	20%
Guinea-Bissau (GNB)	2016	1-29	95.3%	2018	1-3	20%
Kenya (KEN)	2018	1-29	10.1%	-	-	-
Mali (MLI)	2010-2011	1-29	100%	2017	1-6	100%
Mauritania (MRT)	2014	1-29	59.4%	2018	1-5	20%
Niger (NER)	2010-2011	1-29	97.8%	2017	1-7	100%
Nigeria (NGA)	2011-2014	1-29	64.7%	2018	1-6	70%
Rwanda (RWA)	2020	1-29	23.9%	-	-	-
Senegal (SEN)	2012, 2014	1-29	18.8%	2019	1-7	20%
South Sudan (SSD)	2016	1-29	49.2%	2018	1-3	50%
Sudan (SDN)	2012-2013	1-29	94.6%	2016	1-5	100%
Tanzania (TZA)	2020	1-29	9.6%	-	-	-
Togo (TGO)	2014	1-29	57.5%	2019	1-5	20%
Uganda (UGA)	2017	1-29	22.7%	2019	1-3	10%

Table 5.5 Schedule of vaccination with MenAfriVac by country.

where D_a is the number of deaths at age a and L_a is the standard life expectancy at age of death in years. Deaths due to NmA are not explicitly included in the model dynamics. The model reports the number of cases and I applied a 10% case-fatality ratio to the total case estimates. Life expectancy tables were provided by Gavi.

Not all cases of meningococcal meningitis result in death. While some patients survive and continue their lives in full health, disease may also lead to life-long sequelae. The severity of a disease is represented by a factor known as the Disability Weight (DW). The DW can take any value between 0 and 1, where 0 represents full health and 1 represents death. The probability of getting meningitis sequelae is 7.2% and the disability weight (DW) associated with bacterial meningitis is 0.26 [110].

Therefore, the formula for the calculation of YLD is the following:

$$YLD = \sum_{a=1}^{100} [0.072 * (I_a - D_a) * DW * L_a] \tag{5.3}$$

where I_a and D_a are the number of incident cases and deaths at age a, respectively, DW is the disability weight which measures how much the disease affects the survivors and L_a is the life expectancy at age a.

5.6 Results

5.6.1 Cohort size

Initially, I performed a self-consistency check on demography. The population structure in the countries of the African meningitis belt, as can be observed in Figure 5.3, is expected to change in the next 80 years. Using data provided by Gavi, when aggregated across all 26 countries, the median age of the population is expected to increase from 16.4 in 2010 to 33.5 in 2100.

By using country and year specific birth and mortality rates, the model was able to produce demographic figures comparable to those provided by Gavi in the Montagu platform, which were taken from UNPOP. The left panel in Figure 5.4 shows the number of people in each age group over the period 2010-2100 provided in Montagu (unpop), the middle panel represents the cohort size calculated by the model (model) and the right panel represents the absolute difference between the two, calculated as *model - unpop population*. The small positive values in the right panel indicate that the model predicts a slightly higher number of people especially in the older ages. The calculation

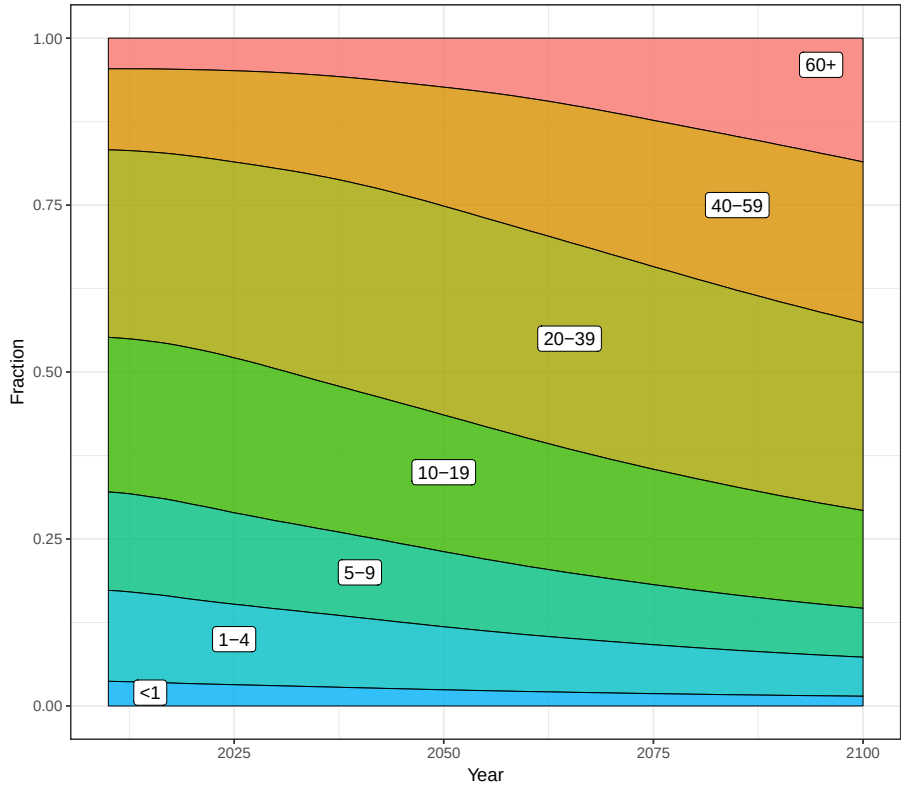


Fig. 5.3 Evolution of age distribution of the 26 countries of the African meningitis belt for the time period 2010-2100.

of UNPOP projections includes migration and it is not simply births minus deaths which is essentially what happens in the model. For that reason, there will be some expected differences between simulated and UNPOP projections.

5.6.2 Fully vaccinated persons (FVPs)

The number of fully vaccinated persons is calculated by multiplying the percentage coverage achieved for each immunisation strategy times the target population. The left panel in Figure 5.5 represents the number of vaccinated individuals in a scenario in which only the initial campaigns take place. All the campaigns take place between 2010 and 2019 with some countries completing the introductory mass campaign over 2 or more years (Table 5.5). The right panel represents the number of fully vaccinated persons when routine immunisation is added to the schedule. The number of vaccinated individuals through routine immunisation increases over time due to increasing birth cohorts.

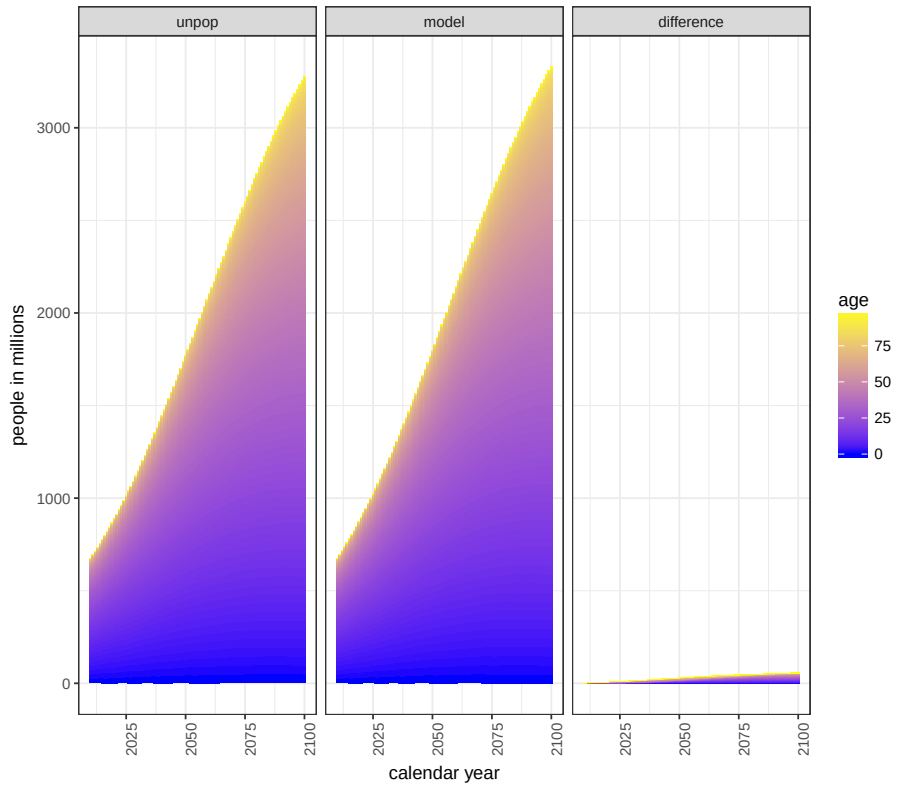


Fig. 5.4 Comparison between actual and simulated population, aggregated across the 26 countries between 2010 and 2100.

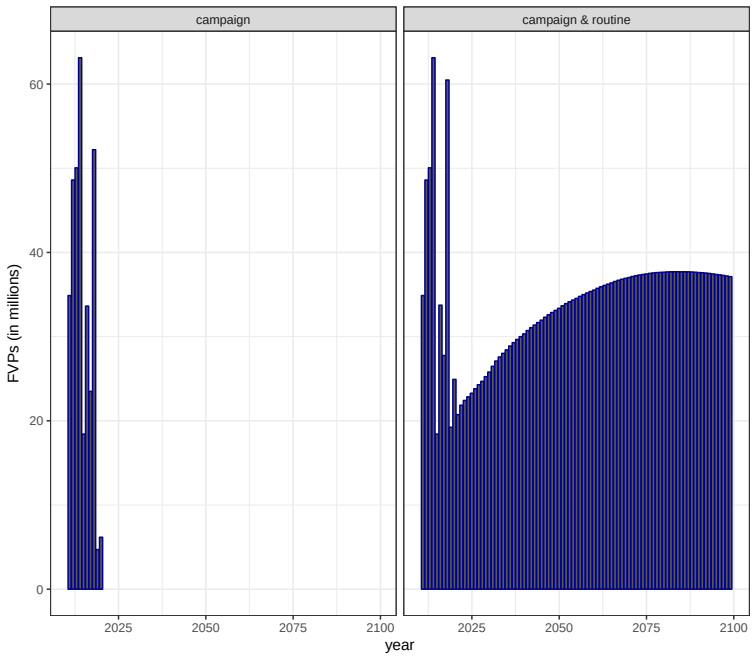


Fig. 5.5 Fully Vaccinated Persons (FVPs) by scenario and by year of vaccination. Aggregated across all countries.

The proportion of the population in the vaccinated compartments over time and by country based on simulation is shown in Figures 5.6 and 5.7.

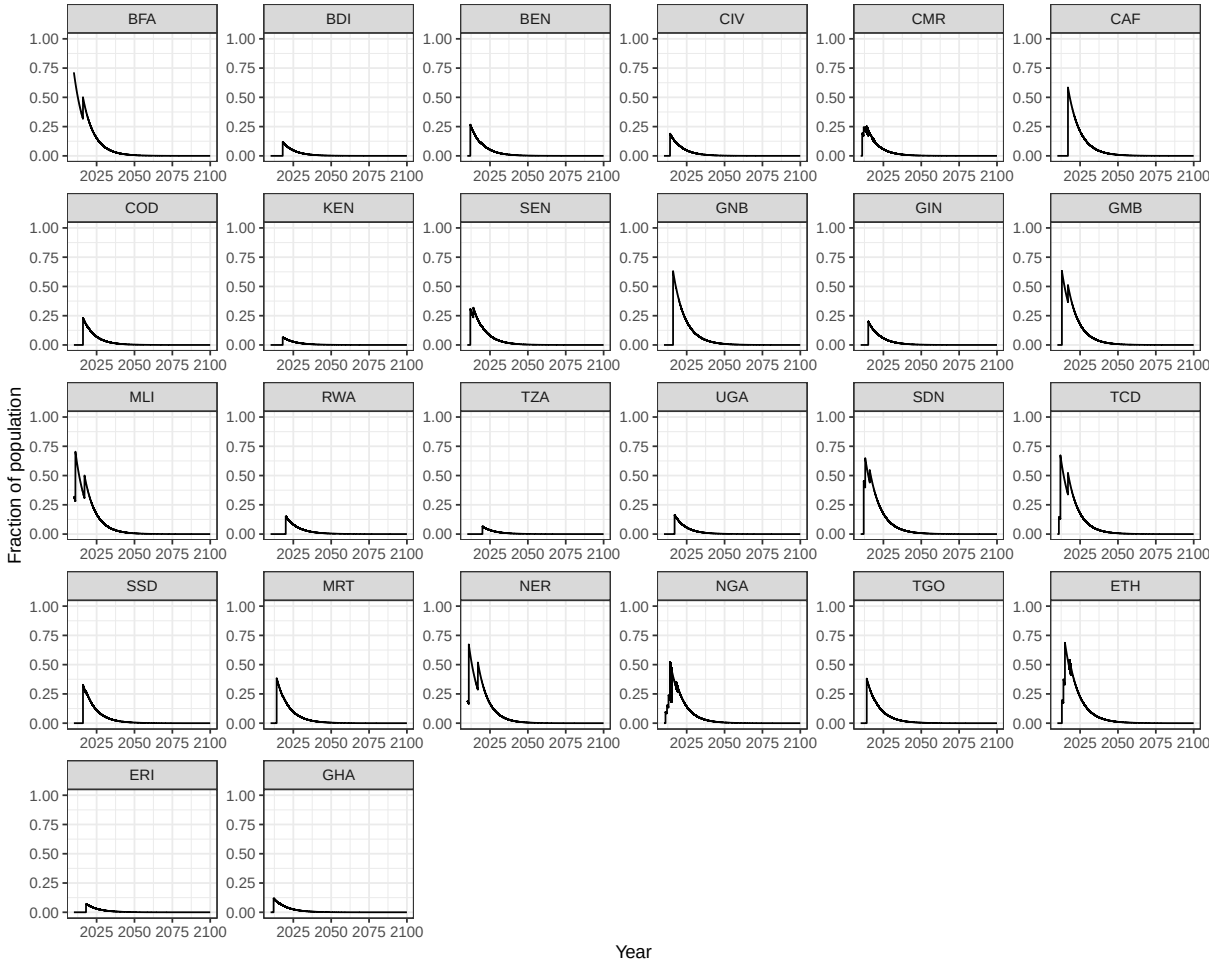


Fig. 5.6 Proportion of people in the vaccinated compartments when only the campaigns take place. Three letter code is used for the names of countries. BDI - Burundi, BEN - Benin, BFA - Burkina Faso, CAF - Central African Republic, CIV - Cote d'Ivoire, CMR - Cameroon, COD - Democratic Republic of the Congo, ERI - Eritrea, ETH - Ethiopia, GHA - Ghana, GIN - Guinea, GMB - Gambia, GNB - Guinea-Bissau, KEN - Kenya, MLI - Mali, MRT - Mauritania, NER - Niger, NGA - Nigeria, RWA - Rwanda, SDN - Sudan, SEN - Senegal, SSD - South Sudan, TCD - Chad, TGO - Togo, TZA - Tanzania, UGA - Uganda.

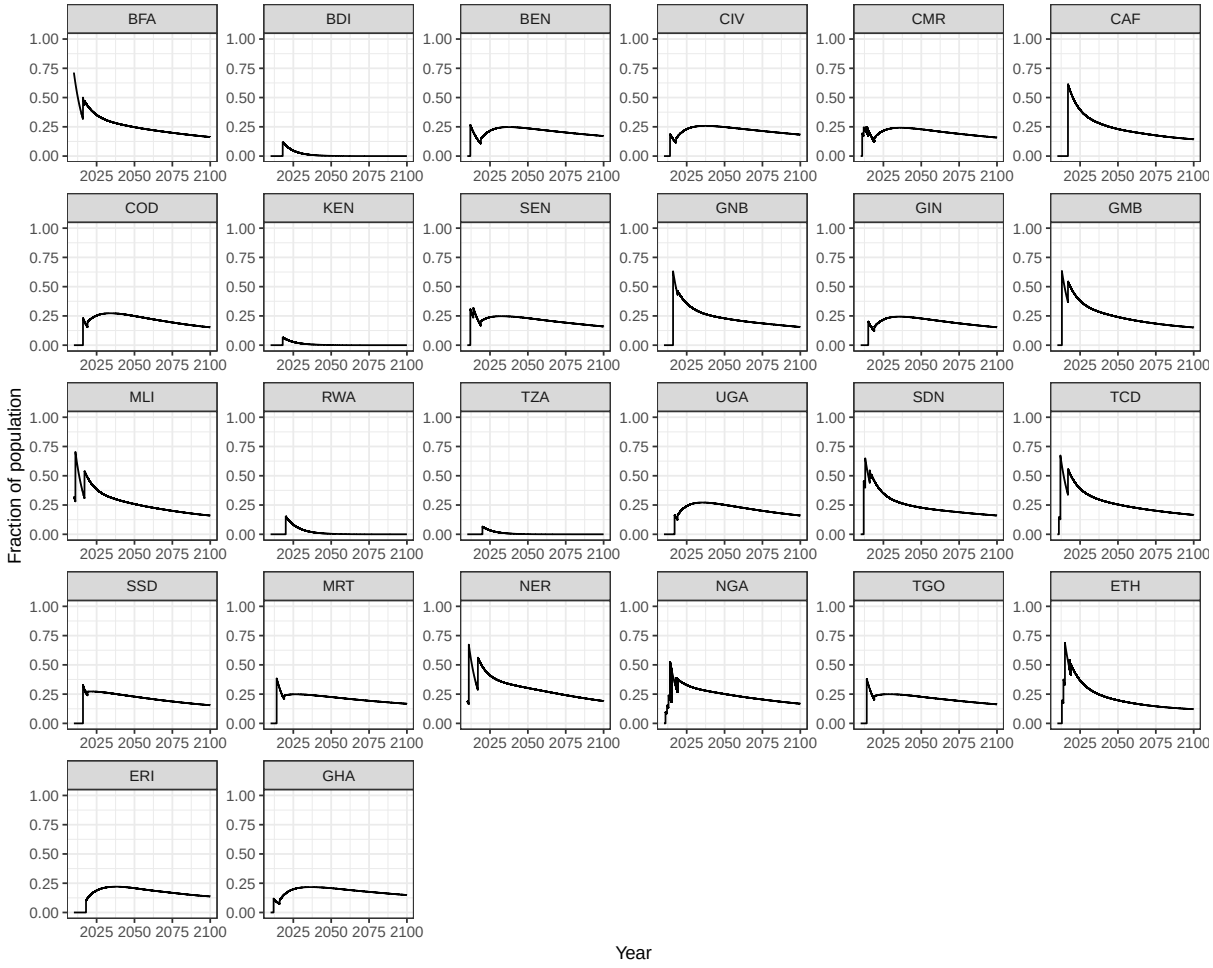


Fig. 5.7 Proportion of people in the vaccinated compartments when both campaign and routine immunisation take place. Three letter code is used for the names of countries. BDI - Burundi, BEN - Benin, BFA - Burkina Faso, CAF - Central African Republic, CIV - Cote d'Ivoire, CMR - Cameroon, COD - Democratic Republic of the Congo, ERI - Eritrea, ETH - Ethiopia, GHA - Ghana, GIN - Guinea, GMB - Gambia, GNB - Guinea-Bissau, KEN - Kenya, MLI - Mali, MRT - Mauritania, NER - Niger, NGA - Nigeria, RWA - Rwanda, SDN - Sudan, SEN - Senegal, SSD - South Sudan, TCD - Chad, TGO - Togo, TZA - Tanzania, UGA - Uganda. Note that coverage for routine immunisation is set to 0% for BDI, KEN, RWA and TZA.

5.6.3 Disease burden

The total burden of serogroup A *Neisseria meningitidis* disease in the African meningitis belt in terms of cases is illustrated in Figure 5.8. The graph shows the average of 200 stochastic model runs and a 95% confidence interval around the mean. The colours

red, blue and green represent countries that are assigned in the high, medium and low category, respectively. Overall, as expected, the model predicts a decline in the number of cases and deaths in the presence of vaccination. The number of deaths is not shown but since they are calculated outside the model by taking a proportion of the cases, the patterns for each outcome are identical, although the scale differs.

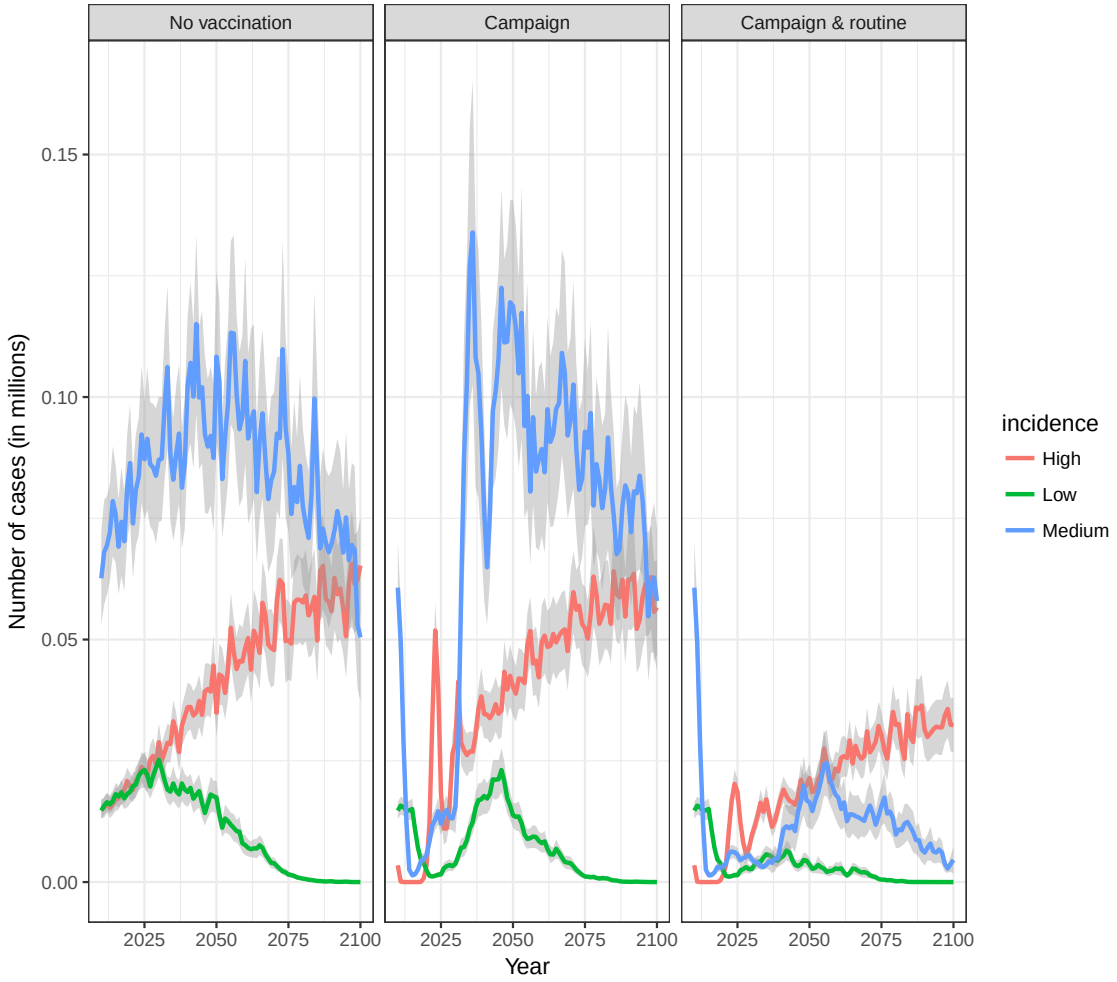


Fig. 5.8 Predicted disease burden across all countries. The solid lines represent the average of 200 simulation runs and the shaded areas show the 95% confidence interval. Different colours represent countries in different incidence categories.

Looking at the left panel in Figure 5.8, in the absence of vaccination, the model predicted an increase in the number of cases for the first 60 years with the number of cases starting to drop after the year 2075. Of the total number of cases, 62% are among people in countries which are classified as medium incidence countries, as opposed to

7.7% in the low incidence countries which are predicted to be free of NmA after 2075. In the early years, the vast majority of cases are predicted in the nine medium-incidence countries. However, as 2100 approaches, the number of cases is more equally distributed between high and medium incidence nations. Plotting the disease incidence over time as opposed to the absolute number of cases, Figure 5.9 shows a constant decline in disease incidence even in the absence of vaccination which explains the drop in the number of cases we can see in Figure 5.8

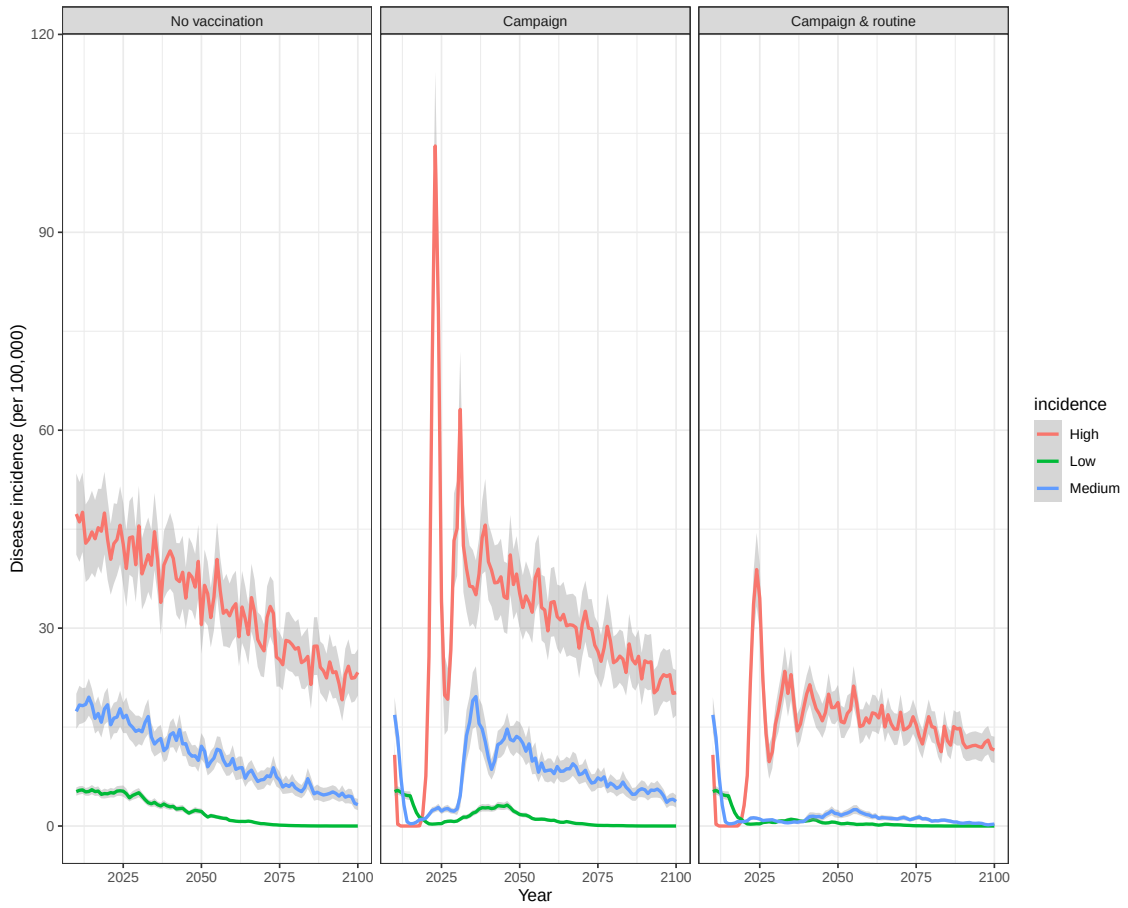


Fig. 5.9 Predicted disease incidence across all countries. The solid lines represent the average of 200 simulation runs and the shaded areas show the 95% confidence interval. Different colours represent countries in different incidence categories.

When only the campaigns take place, middle panel in Figure 5.8, the number of cases drops to very low numbers for around 10 years. The drop is not sharp due to the fact that not all countries immunise their population in the same year. The two high incidence countries, Burkina Faso and Niger, introduced MenAfriVac in 2010, and a resurgence

in those countries is observed which peaks in 2023. An overall increase in the number of cases is predicted around the period 2030-2050, before it starts following the same pattern as the "No vaccination" scenario until 2100.

The far right panel in Figure 5.8 represents the burden of MenA in terms of cases when both campaign and routine immunisation take place. The number of cases is predicted to decrease dramatically if countries introduce MenAfriVac into their routine immunisation schedule. Most cases are seen in the two high-incidence countries, compared to very low level of disease burden in the fifteen low incidence countries.

The country-specific projections of disease burden in the "No vaccination", "Campaign" and "Campaign & routine" scenarios are shown in Figures 5.10, 5.11 and 5.12, respectively. We can see a continuous increase in the number of cases in the two high incidence countries in the absence of vaccination, whereas the model predicts very low levels of disease and even elimination after 50 to 60 years in the low incidence countries.

The total number of cases predicted across all 26 countries of the belt can be seen in Fig 5.13. The aggregation of the results by age and over time is shown in Figure 5.14. The model predicts very few cases in people older than 30 years old in the absence of any vaccination. The highest number of cases is in infants less than one year of age. Looking at the central panel of Figure 5.14 though, we can see that the mean age of infection increases if infants are being routinely immunised. The changes in the age distribution of predicted cases by decades for each scenario can also be seen in Figure 5.15. An increase in the mean age of infection is noted over the years as the population ages even without vaccination.

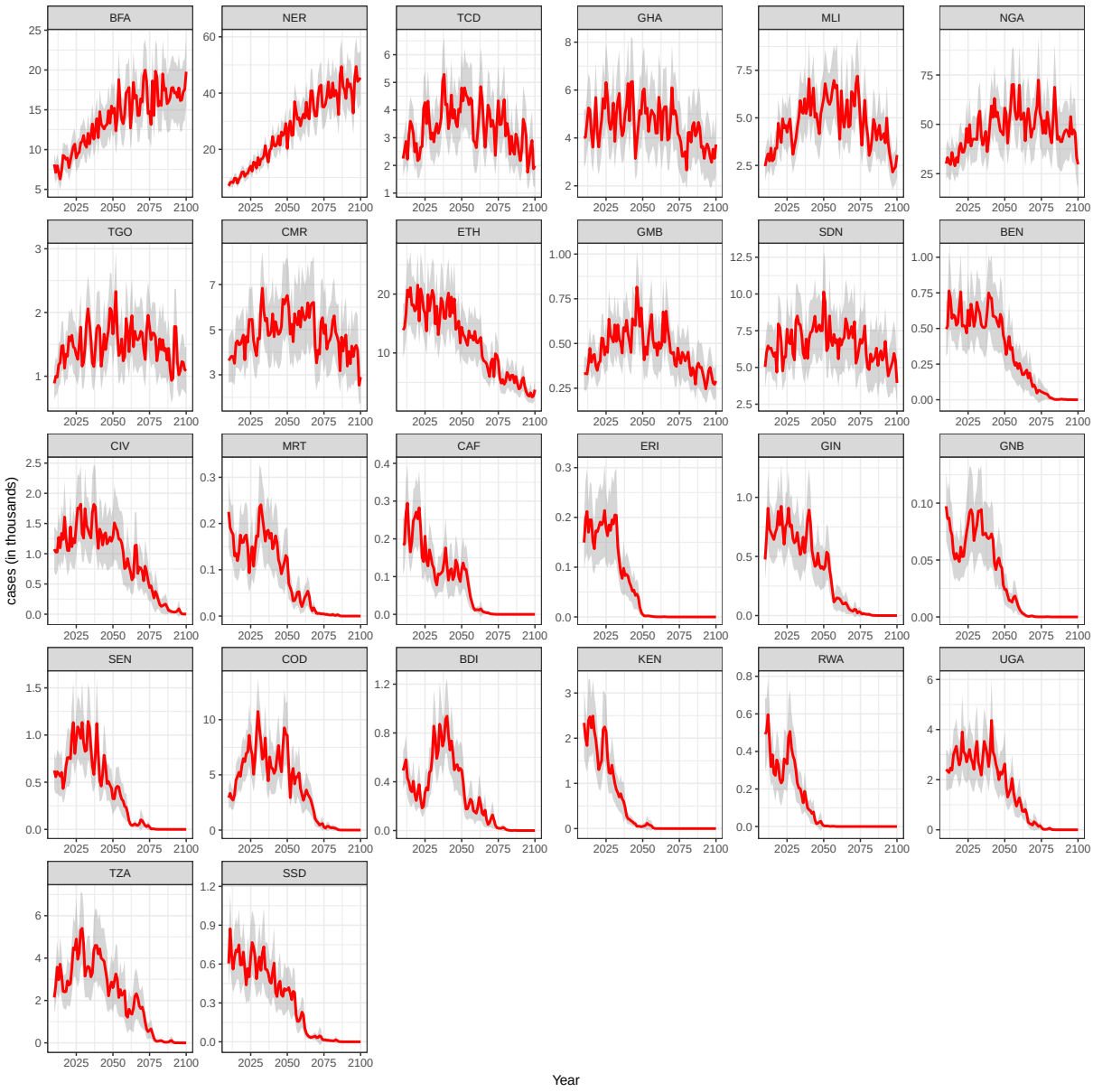


Fig. 5.10 Number of cases predicted for each of the 26 countries of the African meningitis belt in the absence of vaccination. Solid red line represent the mean across 200 simulation runs and shaded are shows the 95% confidence interval. Three letter code is used for the names of countries. BDI - Burundi, BEN - Benin, BFA - Burkina Faso, CAF - Central African Republic, CIV - Cote d'Ivoire, CMR - Cameroon, COD - Democratic Republic of the Congo, ERI - Eritrea, ETH - Ethiopia, GHA - Ghana, GIN - Guinea, GMB - Gambia, GNB - Guinea-Bissau, KEN - Kenya, MLI - Mali, MRT - Mauritania, NER - Niger, NGA - Nigeria, RWA - Rwanda, SDN - Sudan, SEN - Senegal, SSD - South Sudan, TCD - Chad, TGO - Togo, TZA - Tanzania, UGA - Uganda.

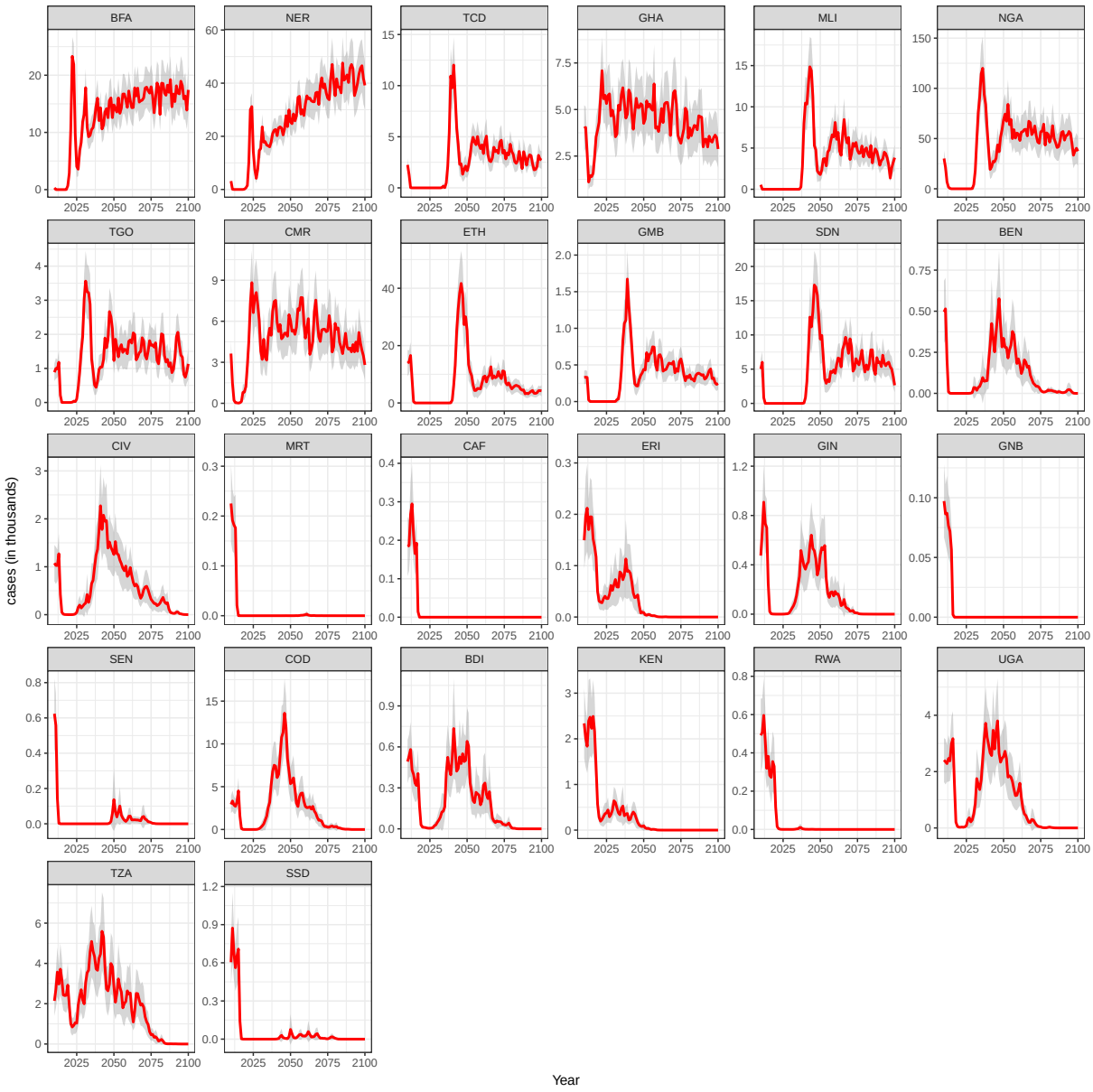


Fig. 5.11 Number of cases predicted for each of the 26 countries of the African meningitis belt if only the campaigns take place. Solid red line represent the mean across 200 simulation runs and shaded are shows the 95% confidence interval. Three letter code is used for the names of countries. BDI - Burundi, BEN - Benin, BFA - Burkina Faso, CAF - Central African Republic, CIV - Cote d'Ivoire, CMR - Cameroon, COD - Democratic Republic of the Congo, ERI - Eritrea, ETH - Ethiopia, GHA - Ghana, GIN - Guinea, GMB - Gambia, GNB - Guinea-Bissau, KEN - Kenya, MLI - Mali, MRT - Mauritania, NER - Niger, NGA - Nigeria, RWA - Rwanda, SDN - Sudan, SEN - Senegal, SSD - South Sudan, TCD - Chad, TGO - Togo, TZA - Tanzania, UGA - Uganda.

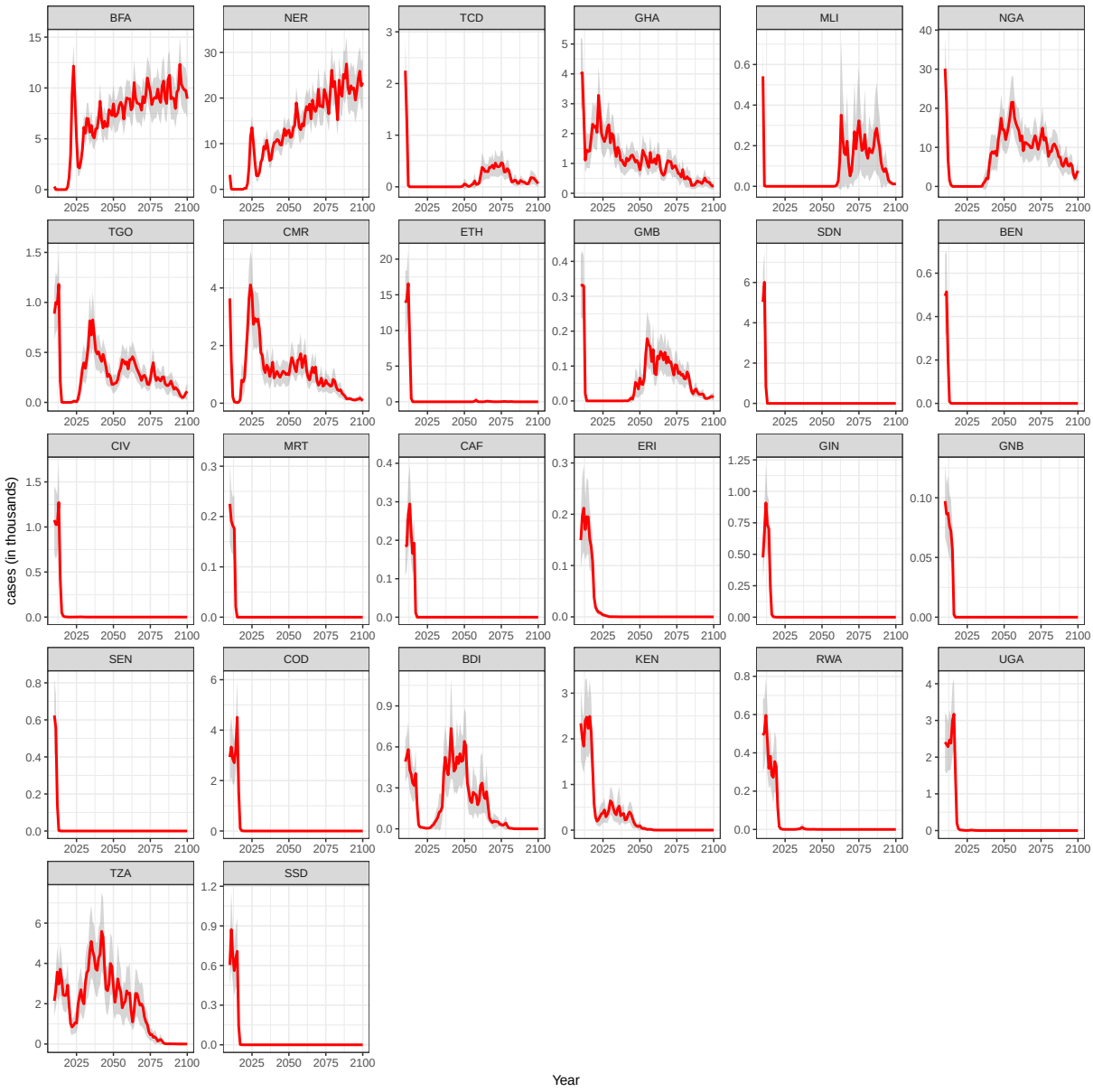


Fig. 5.12 Number of cases predicted for each of the 26 countries of the African meningitis belt if campaigns and routine immunisation take place. Solid red line represent the mean across 200 simulation runs and shaded are shows the 95% confidence interval. Three letter code is used for the names of countries. BDI - Burundi, BEN - Benin, BFA - Burkina Faso, CAF - Central African Republic, CIV - Cote d'Ivoire, CMR - Cameroon, COD - Democratic Republic of the Congo, ERI - Eritrea, ETH - Ethiopia, GHA - Ghana, GIN - Guinea, GMB - Gambia, GNB - Guinea-Bissau, KEN - Kenya, MLI - Mali, MRT - Mauritania, NER - Niger, NGA - Nigeria, RWA - Rwanda, SDN - Sudan, SEN - Senegal, SSD - South Sudan, TCD - Chad, TGO - Togo, TZA - Tanzania, UGA - Uganda. Note that there is no routine vaccination in BDI, KEN, RWA and TZA (see Table 5.5).

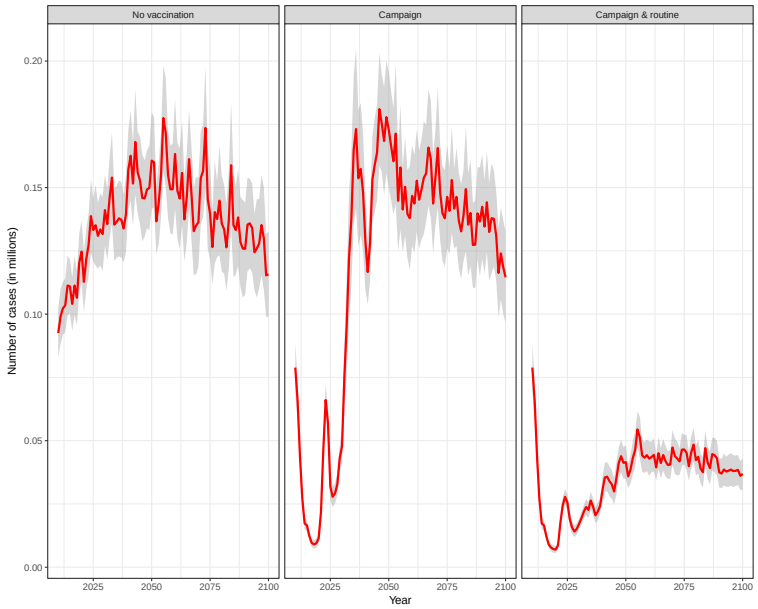


Fig. 5.13 Mean number of cases (red line) by scenario from 200 simulation runs. The grey area identifies the 95% prediction intervals for the predicted values.

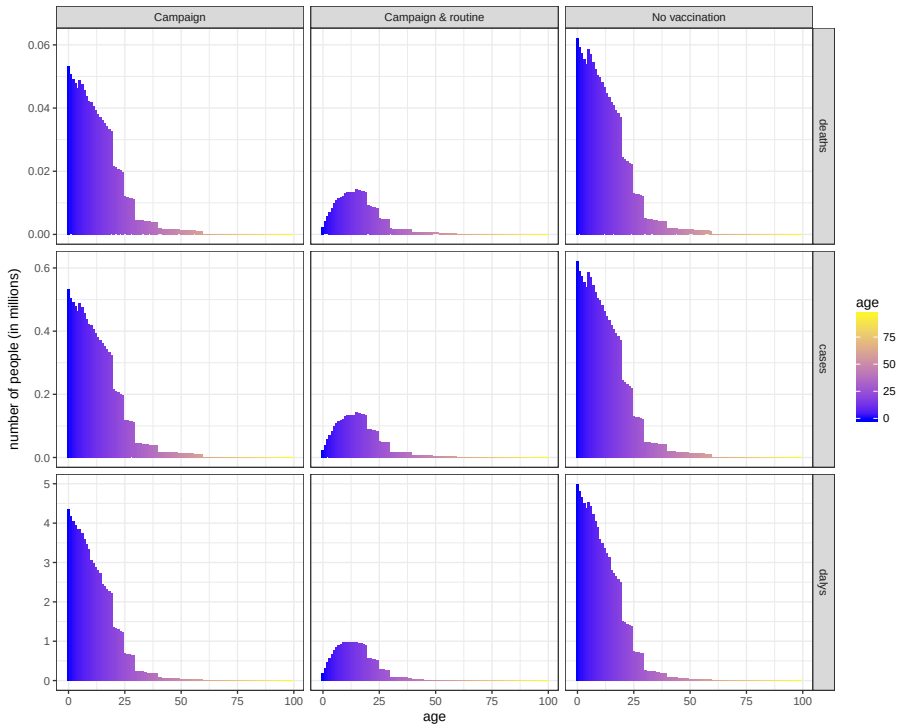


Fig. 5.14 Aggregated (all countries and all years) age distribution by outcome. Averaged across 200 simulation runs.

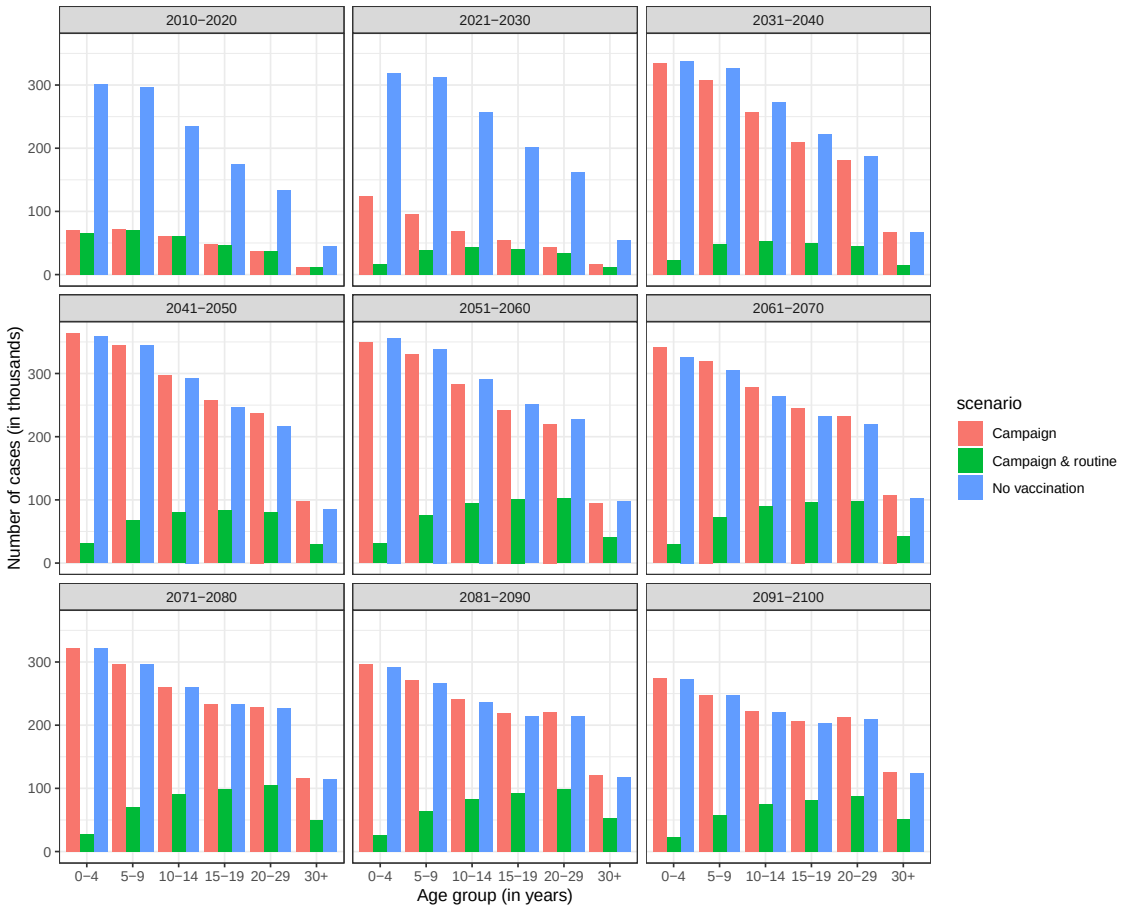


Fig. 5.15 Age distribution of cases across scenario for the time period 2010-2100 divided by decades. Aggregated results across all 26 countries. Average from 200 simulation runs.

The total number of cases, deaths and DALYs for each scenario across all ages and years can be seen in Figure 5.16. If no vaccination takes place, the model predicted a total of 12,532,741 cases across the 26 countries, with 30% of those being in high incidence countries and around 60% in medium incidence countries, compared to 10,817,428 if only the campaigns take place and 3,194,322 cases if MenAfriVac is also introduced into EPI. This difference in the number of cases and deaths translates to more than 60 million DALYs being averted if countries begin to routinely immunise infants some period after the introductory mass campaigns. The numbers used to create Figure 5.16 can be found in Table 5.6.

Scenario	Category	Variable	Value
Campaign	High	deaths	363,436
Campaign & routine	High	deaths	187,373
No vaccination	High	deaths	380,306
Campaign	Low	deaths	62,896
Campaign & routine	Low	deaths	28,850
No vaccination	Low	deaths	96,950
Campaign	Medium	deaths	655,411
Campaign & routine	Medium	deaths	103,209
No vaccination	Medium	deaths	776,019
Campaign	High	cases	3,634,361
Campaign & routine	High	cases	1,873,726
No vaccination	High	cases	3,803,056
Campaign	Low	cases	628,961
Campaign & routine	Low	cases	288,503
No vaccination	Low	cases	969,499
Campaign	Medium	cases	6,554,105
Campaign & routine	Medium	cases	1,032,093
No vaccination	Medium	cases	7,760,185
Campaign	High	DALYs	27,201,378
Campaign & routine	High	DALYs	13,060,327
No vaccination	High	DALYs	28,372,243
Campaign	Low	DALYs	4,445,185
Campaign & routine	Low	DALYs	2,040,673
No vaccination	Low	DALYs	6,754,314
Campaign	Medium	DALYs	45,870,473
Campaign & routine	Medium	DALYs	6,665,070
No vaccination	Medium	DALYs	53,771,984

Table 5.6 Total burden of disease in terms of cases, deaths and DALYs across all ages between 2010 and 2100 for the three scenarios. Average across 200 simulation runs.

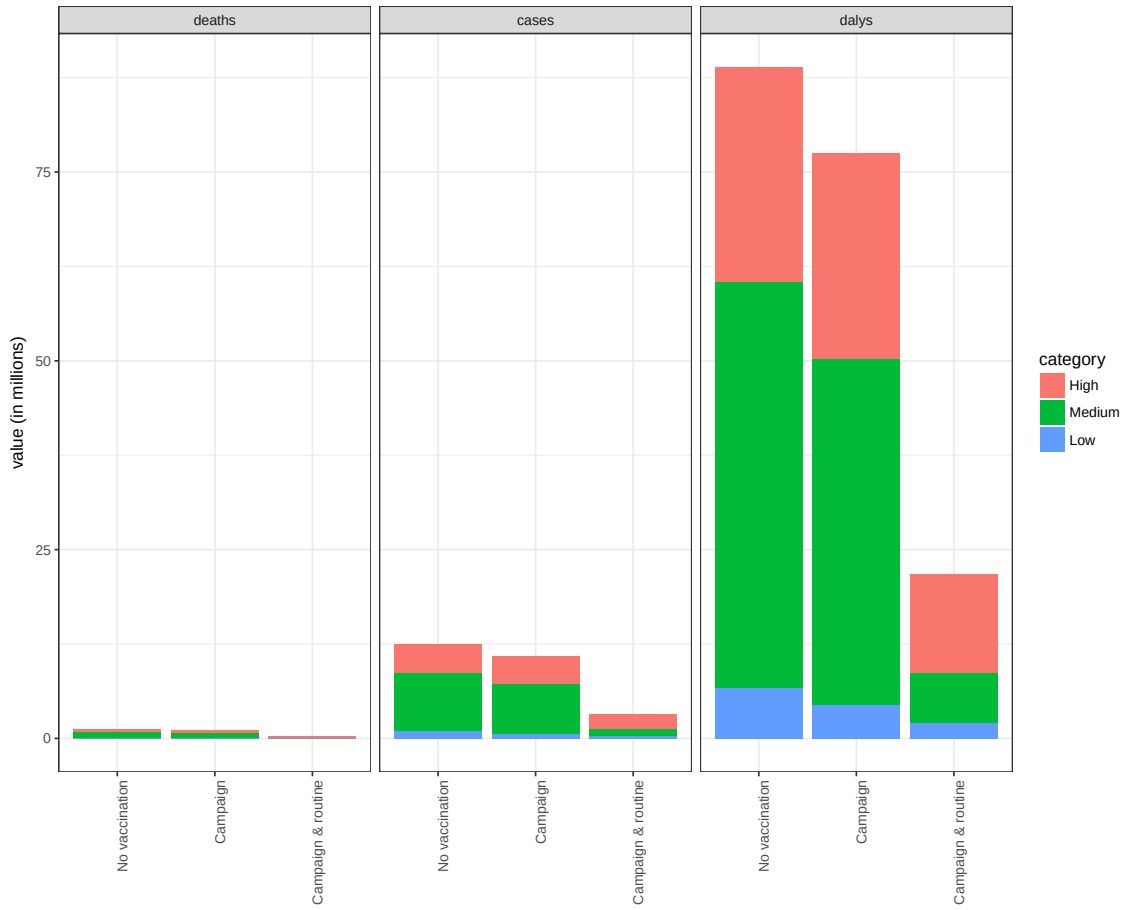


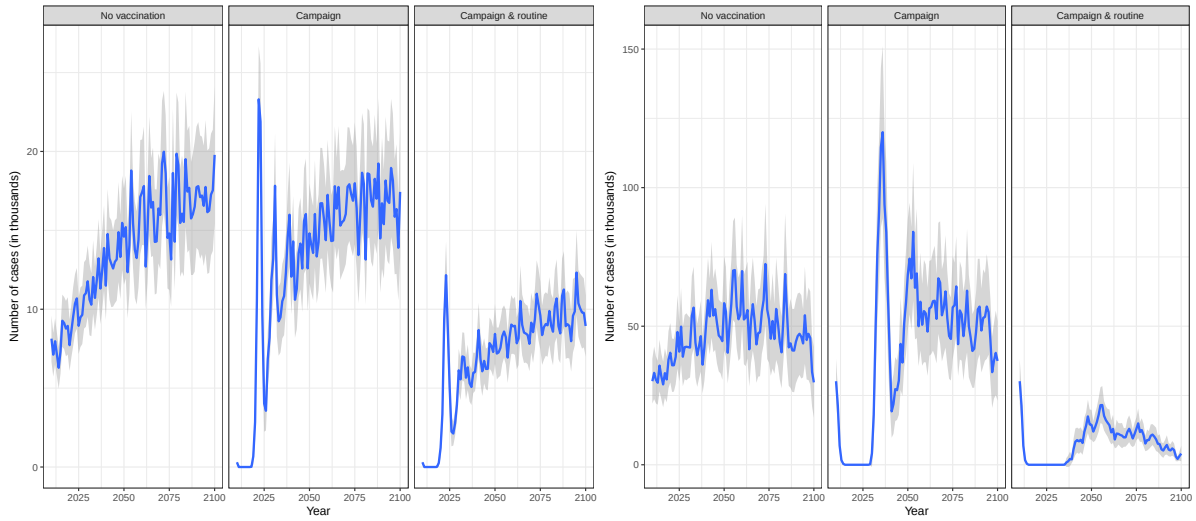
Fig. 5.16 Total burden of disease in terms of cases, deaths and DALYs across all ages by scenario and by category over the period 2010-2100. Average across 200 simulation runs.

5.6.4 Countries with different immunisation schedules

Each country's immunisation schedule has a different impact on the predicted disease burden. Figure 5.17 illustrates the predicted number of cases by scenario in four countries with a different vaccination schedule.

Burkina Faso is one of the two countries in the high-incidence category and as can be seen in Figure 5.17a, a large number of cases is predicted even after the introduction of the vaccine into EPI. This is due to the high levels of transmission in the country. However, the number of cases drop sharply right after the introductory campaign. This sharp drop cannot be seen in the results for Nigeria (Figure 5.17b) due to the fact that the initial campaign takes place over a period of four years instead of just one.

Uganda (Figure 5.17c) and Kenya (Figure 5.17d) are both countries assigned in the low-incidence category. Their main difference is that Uganda is planning to have national routine immunisation while MenAfriVac will be administered through just the initial mass vaccination campaign in Kenya. This lack of routine immunisation results in the number of cases being above zero for approximately 40 years after the introduction of the vaccine compared to zero predicted cases in Uganda.



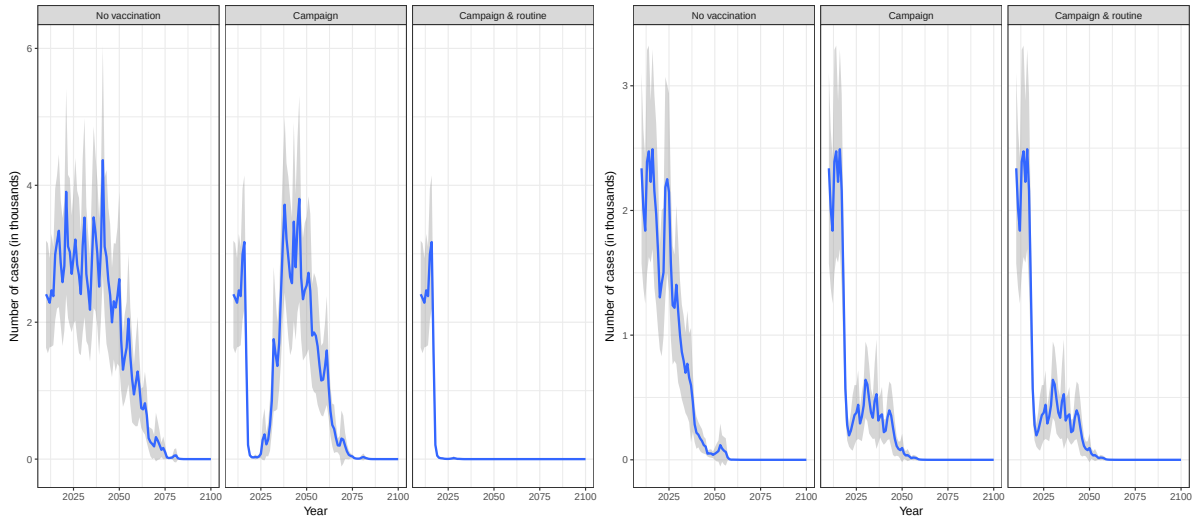


Fig. 5.17 Predicted total mean number of cases (blue line) by scenario in four countries of the African meningitis belt: (a) Burkina Faso, (b) Nigeria, (c) Uganda, (d) Kenya. The grey area identifies the 95% prediction intervals for the predicted values.

5.7 Modelling only the population at risk

The results presented so far in this chapter were generated by running the simulation on the whole population of each country. This is a sensible approach for countries which lie entirely in the meningitis belt. However, as discussed in section 5.4, not all countries are considered to be entirely at risk. For the majority of the countries, disease is affecting only people living in certain parts of the country which is reflected in the proportion targeted for the campaigns in Table 5.5. Here, I run the simulation on only the population assumed to be at risk. To achieve this, I assigned all the areas at risk of the partially in the belt countries in the medium incidence category as defined in the methods. The vaccination coverage was scaled according to the proportion of the population at risk and the proportion of the population targeted in Table 5.5. For example, if proportion targeted was greater or equal to the proportion at risk, I assumed 100% vaccination coverage for the target age group. If proportion targeted was lower than the proportion at risk, the coverage was calculated by diving the number of people targeted by the total number of eligible for vaccination people in the at risk area. I further assumed that routine vaccination takes place only in the parts of the country at risk and is not nation wide as happens in reality.

A comparison of the two approaches is presented in Figure 5.18. Both approaches lead to similar patterns when vaccination occurs with vaccination at the national level leading to smaller in size peak if only the campaigns take place. Modelling only the population at risk, the model predicts a very sharp drop in the number of cases immediately after the initial mass vaccination campaign of 1 to 29 year olds.

In the years after the initial campaign more people are being born and the proportion of people susceptible increases. This increase in the number of susceptible individuals eventually leads to a sharp peak in the number of cases as seen in the previous chapters. On the contrary, the peak is not as large if we assume that vaccination takes place nationally. In this case, 20% vaccination coverage translates to 20% of the population randomly selected for vaccination leaving the rest 80% unprotected. This in turn leads to a slower replenishment of susceptible individuals in the country's total population.

Choosing to use one approach over the other depends on the policy question one wants to address. By modelling only the population at risk, I had to disregard a large number of vaccine doses provided to the countries. In the majority of the cases, the proportion targeted was larger than the proportion at risk, see Table 5.5. Also, the nation wide routine vaccination was not taken into account since I assumed that only

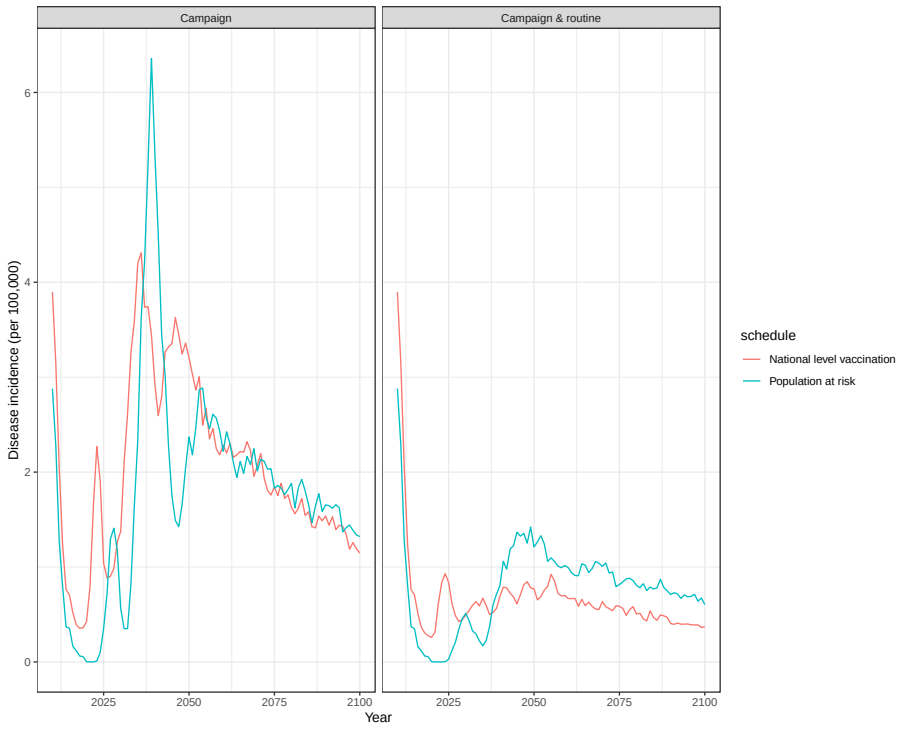


Fig. 5.18 Comparison of predicted disease incidence over the time period 2010-2100 across all 26 countries if simulation runs over the entire country and if it runs only on the population at risk. Average of 200 simulation runs.

children at the age of 12 months who live in the areas inside the meningitis belt receive the vaccine.

5.8 Discussion

To meet the requirements set by the VIMC secretariat, I adapted my initial model, presented in Chapter 3, and I used annual age cohorts instead of 5-year age groups which I had initially used. Furthermore, I used country and year specific birth and mortality rates which resulted in a realistic evolution of the age distribution, compared to the initial stationary age distribution. The stationary age distribution was a fair assumption to make as the model was run for a relatively short time horizon, i.e. 40 years. A stationary distribution though, is not a realistic assumption, and especially for low-income countries such as the countries of the belt. Demographic structure in less developed countries is changing. Life expectancy increases over the years while fertility declines and this leads to older populations. When the model was run for a 90-year period, this change in the

demographic structure resulted in a decline in the predicted annual disease incidence in each country. While the number of cases increases initially, due to the population growth, the incidence drops. This occurs because the proportion of the population in the high risk age groups declines over time as the population becomes older. Subsequently, transmission of disease is reduced because the mixing of the population changes.

Data on historic disease incidence for the majority of the countries is very limited or non-existent and therefore, a decision was made to classify the countries into different categories. After consultation with WHO, I divided the countries based on their geographical location and the available historic data into High-Medium-Low disease incidence countries. According to WHO, most countries were only partially targeted for the introductory mass campaigns. In the coverage sets provided by the secretariat, the coverage for the mini catch-up campaigns was assumed to be the same as the fraction of the population in each country that is considered to be at risk of meningococcal meningitis. However, for a number of countries, such as Guinea-Bissau and Central African Republic, the coverage achieved during the initial mass campaigns is surprisingly high and it is not clear why this is the case. Although for some countries the mass campaigns take place at a sub-national scale, routine immunisation is assumed to occur nationwide.

The model was run for the time horizon 2010-2100 and recorded the number of cases deaths and DALYs by year, age and country under three immunisation scenarios. The results for the scenario in which routine immunisation together with a mini catch-up campaign following the introductory campaign targeting 1-29 year olds were compared with the results under a no vaccination scenario and a scenario in which only the campaigns take place. When aggregated across all countries, the model predicted that the use of MenAfriVac in the long-term will prevent more than 9 million cases until the year 2100.

The fact that NmA cases are not eliminated even after routine vaccination of babies suggests that this immunisation strategy may not be the most effective in the long run. Assuming that vaccine protection lasts for an average of 10 years, most vaccinated children will lose protection while they are still in the high risk age groups. Additionally, recent data also suggest that protection wanes faster in individuals vaccinated at a very young age. Thus, it is worth exploring alternative immunisation strategies such as targeting school children for routine vaccination.

The results of this work were consistent with the results from the initial model, that suggested that unless MenAfriVac is introduced into routine immunisation, there will

be a strong resurgence in disease incidence after a honeymoon period following the initial mass campaigns. This resurgence cannot be seen clearly in the aggregated results because countries introduce MenAfriVac at different times and over the course of ten years. However, looking at the results for each country individually, one can see the effect which the vaccine has on their population. For countries in the Low incidence group, the number of cases drops to very low numbers even with no vaccination. This is caused solely by the shift in the age distribution of the population over time.

One of the limitations of this work is that it is not possible to validate the model predictions. Vaccination started in 2010 and that translates to only eight years of data from Burkina Faso. All data from studies looking at MenAfriVac impact support an extended period of very low incidence immediately after the mass campaigns [108, 63, 73, 111].

In the Investment Case submitted by WHO in 2008, the vaccine impact estimates were based on models that used data from one population-based study in Niger. The vaccine impact for a ten year period was estimated for only seven countries assuming that they all have the same levels of incidence. The model was static and assumed that there was one epidemic every ten years. According to published studies, Niger, together with Burkina Faso, has very high levels of incidence compared to the rest of the countries of the belt. For that reason, by assuming that all countries have the same high incidence rates, the impact presented in the Investment Cases was most likely an overestimation of the true impact. This model was initially used by Gavi to estimate MenAfriVac impact. Our model is thus an improvement in several respects since it is a dynamic transmission model which uses country-specific demography.

Understanding that every mathematical model has its strengths and limitations, the secretariat sub-contracts two modelling groups to develop models for the same disease and they are asked to produce the same output. Having two models for the same disease can offer a better view on the uncertainty around the model structure and the assumptions made during the simulation runs by the modellers (see Chapter 4).

This exercise supports the huge investment in MenAfriVac as it shows that the potential benefits of MenAfriVac immunisation in reducing mortality and morbidity across the African meningitis belt are tremendous. Nonetheless, it is important to emphasize the effect of protecting newborn cohorts after the initial campaigns have been completed. The routine immunisation of children with MenAfriVac might make it possible to eliminate epidemic Group A meningitis in sub-Saharan Africa.

Chapter 6

Simulating alternative vaccination strategies and understanding the role of duration of vaccine protection

6.1 Introduction

Considerable reductions in meningitis incidence have been observed following the introduction of MenAfriVac. A study published in 2017 shows a 99% decline in the number of confirmed group A cases in fully vaccinated populations [108]. However, the work presented in the previous chapters suggests that routine immunisation of babies under the age of 12 months may not be the optimum long-term strategy. This is due to waning of protection by the teenage years, when there is still heightened risk of meningitis. Additionally, recent studies show that vaccination later in childhood offers higher levels of antibodies that persist for longer [75].

It is not uncommon for a country to change its immunisation schedule based on new data and the continued monitoring of the situation. For example, the MenC vaccination schedule in the UK has changed several times since its introduction in 1999 [112]. The MenC vaccine was initially administered to babies in 3 doses at the ages of 2, 3, and 4 months. Then, in 2006, it changed to two doses at the age of 3 and 4 months followed by a booster dose at 12 months. To maintain high levels of herd immunity, a further booster dose targeting teenagers aged 13-15 years was introduced in 2013. In 2015, the

Joint Committee on Vaccination and Immunisation recommended that the infant dose at three months should be dropped [113], so that the current schedule is one dose at 12 months followed by a booster dose at 13-15 years.

When making recommendations about a vaccine schedule, the aim is to provide the best possible protection to the population through the smallest number of vaccine doses given at most effective times.

In this chapter I explore how the optimal vaccination strategy may change in the long term. Specifically, I consider four scenarios that could be plausible alternative strategies to the current.

6.2 Demographic model

I used the existing model, presented in Chapter 3 and adapted in Chapter 5, which reproduces the country-specific epidemiology of NmA in the pre-vaccination era, to project the burden of disease under a number of alternative vaccination schedules in the years after MenAfriVac introduction. Demographic data for Chad were used to estimate parameters for the model. The total population of Chad is expected to increase a 4-fold according to UNPOP during the time period 2010 - 2060, as plotted in Figure 6.1 which shows the change in the number of total population size (Left panel in Figure 6.1) as well as the change in relevant age groups over time (Right panel in Figure 6.1). In the model I used year-specific birth and mortality rates obtained from UNPOP to model population growth.

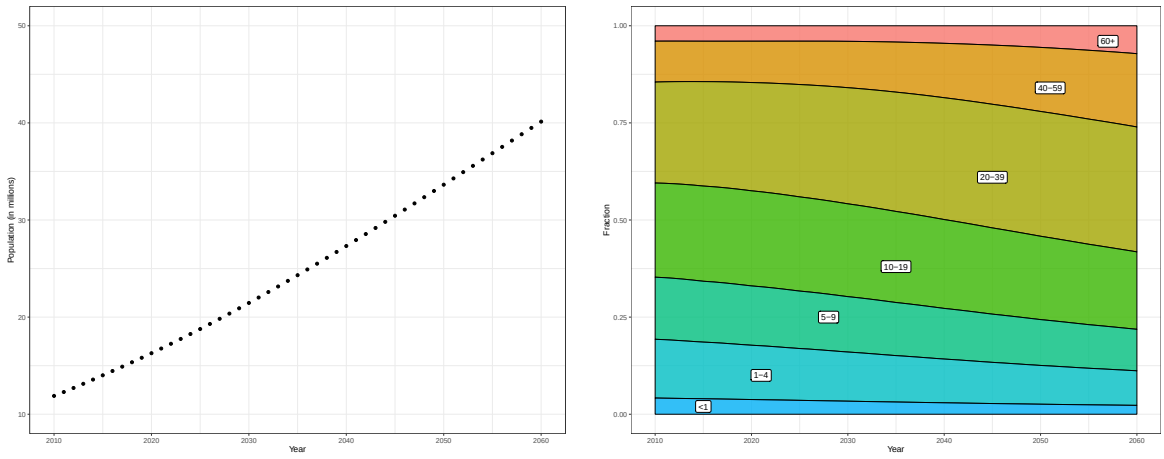


Fig. 6.1 Changes in the population of Chad during the time period 2010-2060. Left panel: Total change in population size. Right panel: Evolution of age distribution over time.

Epidemics of MenA in Chad in the pre-vaccine era occurred every 8-12 years as previously described in Figure 2.1, which is representative of the epidemiology of NmA in the African meningitis belt. The introduction of MenAfriVac in that country was completed in two phases during 2011 and 2012. People between 1 and 29 years of age in three regions, consisting of 20% of the total population of 1-29 year olds in Chad, were targeted during the initial phase in 2011 while vaccination of individuals of the same age group in the rest of the country followed one year later. Figure 6.2 shows the dramatic effect of vaccination on the annual incidence of suspected and laboratory confirmed cases of bacterial meningitis per 100,000 in Chad. Note that the incidence in Figure 6.2 represents all *Neisseria meningitidis* serogroups and not only serogroup A which is affected by MenAfriVac.

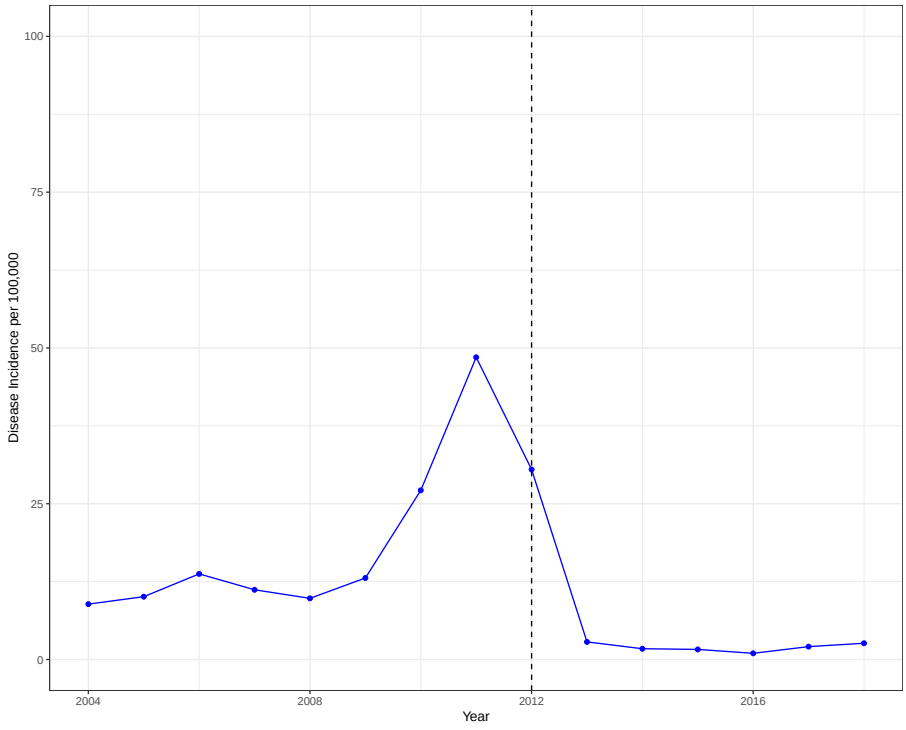


Fig. 6.2 Annual incidence of suspected and confirmed cases of bacterial meningitis per 100,000 in Chad. Year of completion of MenAfriVac initial mass vaccination campaign indicated by dotted line. Data taken from WHO weekly meningitis reports [1].

For simplicity in the model, I assumed that 50% of those aged between 1 and 29 years of age were targeted in 2011 while the remaining 50% received the vaccine in 2012. In 2012, those that had not been vaccinated and turned 30 were no longer eligible and children under 12 months of age in 2011 became available for selection.

6.3 Immunisation schedules assessed

The scenarios outlined below were elucidated through informal discussions with colleagues at WHO, PATH and CDC to be of interest. Children and young adults are the people in the highest risk age groups, as seen in Figure 3.3, and this is why routine immunisation at 5 and 10 years were chosen as possible alternative strategies. All routine programmes are assumed to start taking place either 5 or 10 years after the second phase of the initial mass campaign of 1-29 year olds in 2012. The mass campaigns in 2011 and 2012 are modelled as discrete time events taking place at one point in time.

Strategy EPI@12m (current strategy)

Start of routine immunisation at 12 months in 2017 together with a mini catch-up campaign of children aged between 1 and 6 years.

Strategy EPI@5y

Routine immunisation of children when they reach the age of 5 years starting in 2017 (i.e five years after the introduction of MenAfriVac). This five-year delay allows children to reach the target age group for routine vaccination without having received a vaccine dose at an earlier age through the initial mass campaign.

Strategy EPI@10y

Routine vaccination targets children when they become 10 years old which is assumed to start ten years after the completion of the initial campaign (i.e in 2022). No catch-up campaign is assumed to take place during the period 2012-2022.

Strategy Booster

Starting in 2017, children receive two doses of MenAfriVac. The first one at the age of 12 months followed by a booster dose at the age of 5 years.

Strategy Switch

This scenario aims to reflect what would happen if the current schedule was changed and routine vaccination started targeting 5 year olds instead of children at the age of one. In a real life scenario, one would not expect the switch to happen instantaneously and thus I assumed that for a period of 5 years children are given two doses. One at the age

of 12 months and a booster dose at the age of 5 years. After this intermediate period I assume that the dose at 12 months is dropped and only 5 year olds are targeted for routine vaccination.

6.3.1 Duration of protection

Once the model is developed, the identification of the most effective scenario is not trivial. Examination of vaccine associated parameters can alter the conclusions regarding the best long-term strategy. An important vaccine parameter is the duration of protection offered by MenAfriVac. All the model runs presented in the previous chapters were done under the assumption that vaccine induced protection lasts for an average of ten years.

To account for the uncertainty around the duration of protection, I ran the model under four different scenarios:

- 5 years duration of protection for all ages.
- 10 years duration of protection for all ages.
- 20 years duration of protection for all ages.
- 5 years duration of protection for <5 year olds and 10 years duration of protection for children >=5 years.

6.3.2 Model modification

A model modification was necessary in order to simulate an age-dependent duration of protection. I added four new compartments to the existing model, namely SE, CE, IE, RE. These four states represent the susceptible, carriers, diseased and recovered/immune who receive vaccination at an early age. A list of all the compartments in the model and their definitions is provided in Table 6.1.

Children vaccinated up to the age of five years, get transferred to those compartments while children who are targeted after they have had their fifth birthday are moved to the SV, CV, RV compartments accordingly. For example, during the initial mass campaign, children in the age groups 1 to 2 year, 2 to 3 years, 3 to 4 years, 4 to 5 years are transferred to the early vaccination compartments (SE, CE, RE) while individuals between 5 and 29 years of age are moved to the vaccinated compartments (SV, CV, RV). Note that there is no movement to the IV or IE compartment upon vaccination as I assume that individuals with meningitis do not receive a vaccine dose. Individuals in the vaccinated

Compartment name	Definition
S	Susceptible individuals not vaccinated
C	Carriers of NmA not vaccinated
I	Individuals with invasive disease not vaccinated
R	Immune after colonisation or disease not vaccinated
SE	Susceptible individuals vaccinated with MenAfriVac before the age of 5 years
CE	Carriers of NmA vaccinated with MenAfriVac before the age of 5 years
IE	Diseased individuals vaccinated before the age of 5 years
RE	Immune after colonisation or disease vaccinated before the age of 5 years
SV	Susceptible individuals vaccinated with MenAfriVac after the age of 5 years
CV	Carriers of NmA vaccinated with MenAfriVac after the age of 5 years
IV	Diseased individuals vaccinated after the age of 5 years
RV	Immune after colonisation or disease vaccinated after the age of 5 years

Table 6.1 List of the model compartments and their definitions.

states (SE/SV, CE/CV, IE/IV, RE/RV) revert to the equivalent unvaccinated S, C, I, R states at the age-specific rate depending on the strategy implemented.

With the addition of the extra compartments, the force of infection for age group j becomes

$$\lambda_j = \theta \sum_{k=1}^{100} \beta(z_j, z_k)(I_k + C_k + IV_k + CV_k + IE_k + CE_k)$$

where θ is the stochastic term which changes annually and $\beta(z_j, z_k)$ is the transmission rate between age groups j and k.

The system of differential equations used to simulate each vaccination scenario can be found in Appendix C.

6.3.3 Vaccination coverage

According to Gavi's operational forecast, the coverage in Chad for routine immunisation of infants starts at 75% in 2017 and continues with annual increments of 1% until it reaches the 90% mark. It is then assumed to stay constant for the remaining years. This coverage has been used to generate the results in Chapter 5. However, determining what the coverage would be if the target age of routine immunisation is 5 or 10 years is not straightforward since there is no vaccine currently being administered at these ages in African countries. I explored the impact of vaccination assuming a high coverage of 80% and a low coverage of 50%.

6.3.4 Measuring vaccine impact

The model is run for the time period 2010-2060 using a daily time step. For each model run, the number of cases by age is calculated per year. The average number of cases and the percentage of cases prevented by each of the strategies is calculated over 200 simulation runs per strategy. To account for the uncertainty due to the stochastic nature of the model, a 95% confidence interval of the mean is also calculated using the t.test function in R.

To allow for a comparison between the different strategies, the model was set to keep track of the time to resurgence, median age of infection and the age distribution of cases for each strategy and for each assumption regarding both the duration of protection and vaccine coverage. As resurgence I defined the time it takes for the incidence to reach 100 cases.

When comparing vaccination strategies it is important to understand the potential benefits of each strategy. The number of cases predicted is a measure but it is often not enough alone. Another helpful measure which illustrates the impact of vaccination on the population is the number of people needed to vaccinate (NNV) to prevent one case. NNV as a measure of efficiency has been widely used in the literature [114]. In this case, NNV is defined as the total number of doses administered divided by the total number of cases prevented under each vaccination strategy over the time period under consideration. The total number of doses given for each scenario was calculated by multiplying the total number of people targeted with the assumed age-specific vaccine uptake. The number of cases prevented for each scenario is calculated as # cases with no vaccination - # cases predicted for each scenario.

6.4 Results

6.4.1 Baseline Scenario (EPI@12m)

Results in this section are in the baseline scenario assuming a mean duration of protection of 10 years and 80% vaccine uptake for children routinely immunised over the age of 12 months. The numerical results for the different strategies are shown in Table 6.2. The results in this section are also presented graphically in the following sections which focus on the comparison of the strategies. The model results suggest that in the baseline scenario, routine vaccination aimed at school children is not better than routine immunisation of one year old children. However, switching the age at vaccination from 12 months to 5 years is the single dose strategy with the lowest average number of cases predicted. The strategy which leads to the largest number of cases averted is the Booster strategy with a 79.3 (95% CI: 78.7-79.8) predicted overall reduction.

6.4.2 Number of vaccinated individuals

The immunisation schedules under consideration may all start with the same introductory mass campaign, but the target population for routine immunisation is different. This leads to differences in the number of people predicted by the model to be in the vaccinated states and therefore assumed to be protected against carriage and disease. The time-series plot in Figure 6.3 shows the proportion of people in the vaccinated compartments over the 50 year time horizon between 2010 and 2060. All strategies start with the same number of immunised individuals but over time, this changes according to the schedule and the target population. Longer duration of protection results in a greater proportion of people in the vaccinated states as they stay there for longer periods. Vaccinated individuals start appearing in 2011 during the first phase of the MenAfriVac introduction which is completed the following year. The secondary peak which can be seen in Figure 6.3 in the year 2017 represents the mini-catch-up campaign which takes place at the start of the routine immunisation of 1 year olds.

6.4.3 Time to resurgence

Figure 6.4 shows the average number of cases predicted during the 50-year period across the different schedules as well as the different assumptions about the duration of protection. The scenario in which there is no further vaccination after the mass campaign is also plotted in Figure 6.4 for comparison. An average of 3,531 (95% CI: 2,645-4,418)

	Scenario					
Outcome	**No vaccination** n(95% CI)	**Current Strategy (EPI@12m)** n(95% CI)	**EPI@5y** n(95% CI)	**EPI@10y** n(95% CI)	**Switch** n(95% CI)	**Booster** n(95% CI)
Total number of cases (in thousands)	260.7 (258-263.4)	86.3 (84.6-88.1)	87.6 (85.8-89.3)	87.1 (85.1-89.2)	77.3 (75.1-79.5)	54.1 (52.5-55.6)
Cases averted (in thousands)	-	174.4 (171.8-176.9)	173.1 (170.7-175.5)	173.5 (171.1-176)	183.4 (181-185.8)	206.6 (204.3-209)
% of cases averted	-	66.8 (66.2-67.4)	66.4 (65.8-67)	66.6 (65.9-67.2)	70.4 (69.7-71.1)	79.3 (78.7-79.8)
Year of resurgence	-	2032	2030	2027	2034	2031
Total number of doses (in millions)	-	42.03	33.87	30.02	39.96	63.88
NNV	-	243	198	175	220	311

Table 6.2 Numerical results for the different vaccination scenarios. Duration of protection is 10 years and vaccine uptake is assumed to be 80% for children routinely immunised over the age of 12 months.

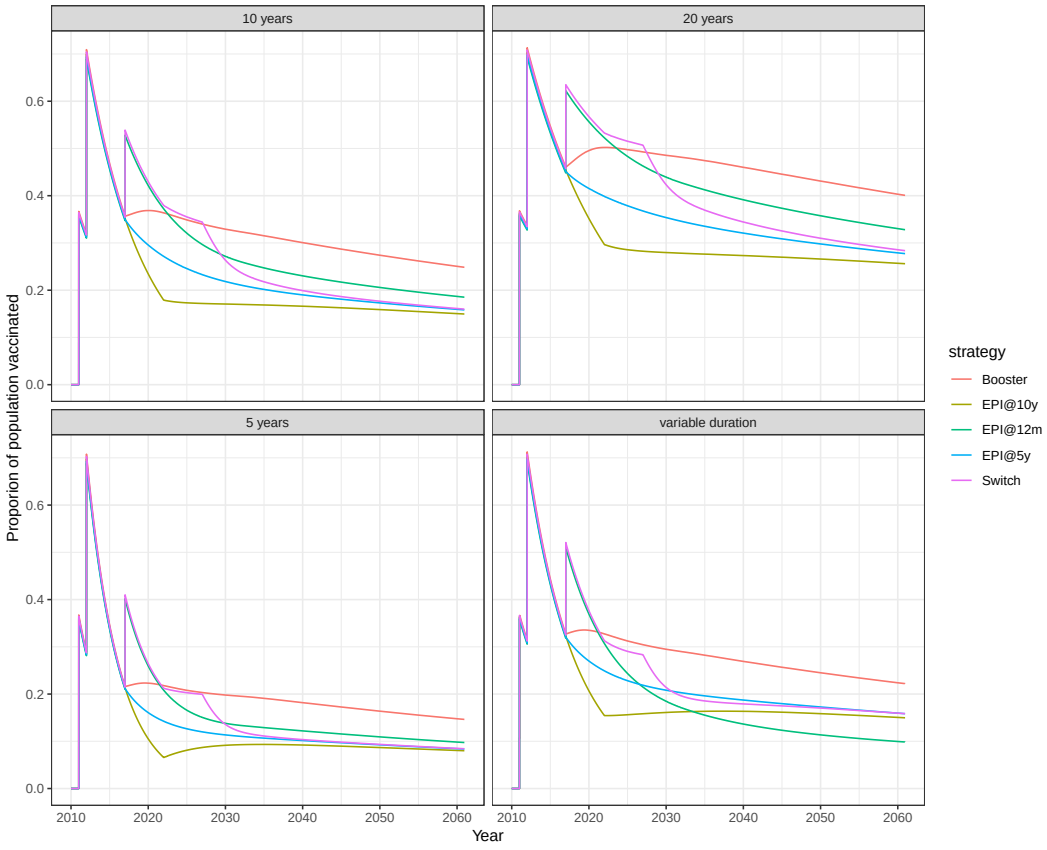


Fig. 6.3 Proportion of population vaccinated over time for each vaccination strategy and for each assumed duration of vaccine protection.

cases are predicted in the year prior to MenAfriVac introduction. This number drops to 662 (95% CI: 472-852) cases in 2011, the year in which half of the population aged between 1 and 29 years receive a vaccine dose.

The model also predicts that when the assumed duration is other than 20 years for all ages, a resurgence always follows the initial mass campaigns. The size of the peak as well as the year of resurgence both depend on the schedule and the duration of protection. No cases are predicted for at least 50 years if duration of immunity provided by the vaccine is assumed to last for an average of 20 years.

Also, the longer the duration of protection, the longer the predicted honeymoon period is. This can be better seen in Figure 6.5 which shows the total number of cases plotted against the year of resurgence for each scenario and for the different assumptions regarding the duration of protection and coverage. Note that the year shown in Figure 6.5 is not the year of the peak but the year in which the number of cases starts to increase

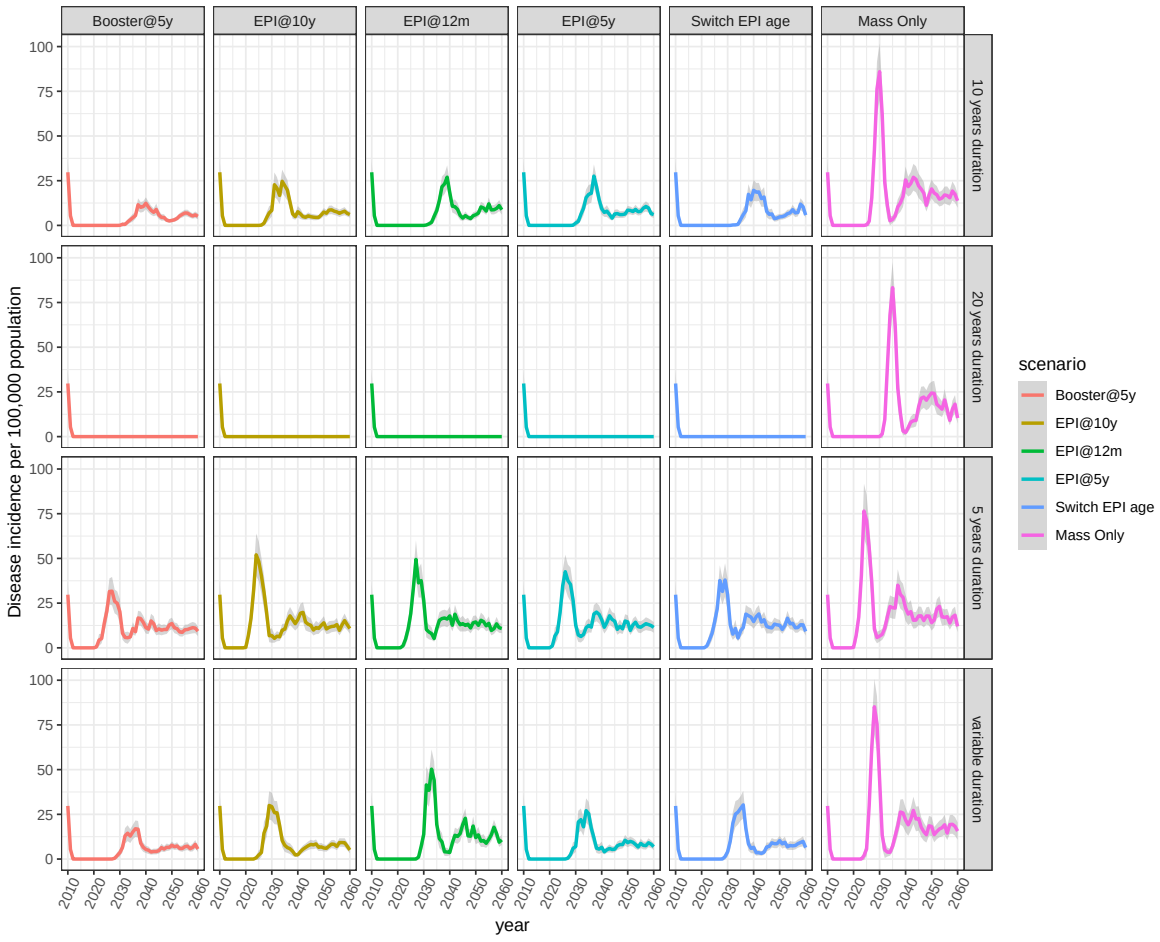


Fig. 6.4 Average disease incidence across the different vaccination scenarios and across the different assumptions regarding the duration of vaccine induced protection. Assumed coverage for schoolchildren vaccination is 80%. Shaded areas represent the 95% confidence intervals.

following the zero incidence years as a result of the introductory campaign. Also, since the model does not predict a resurgence when vaccine induced protection is assumed to last for an average of twenty years, the results for 20 years duration of protection are not shown in Figure 6.5.

If we assume that the duration of protection is five years regardless of the age at vaccination, the model predicts that the number of cases will start increasing only ten years after the introduction of MenAfriVac, compared to 20 years of honeymoon period when duration of protection is 10 years. However, routine immunisation at 12 months with a booster dose at 5 years is the strategy with the lowest number of cases predicted. Earlier resurgence does not necessarily translate to a larger number of total cases. For

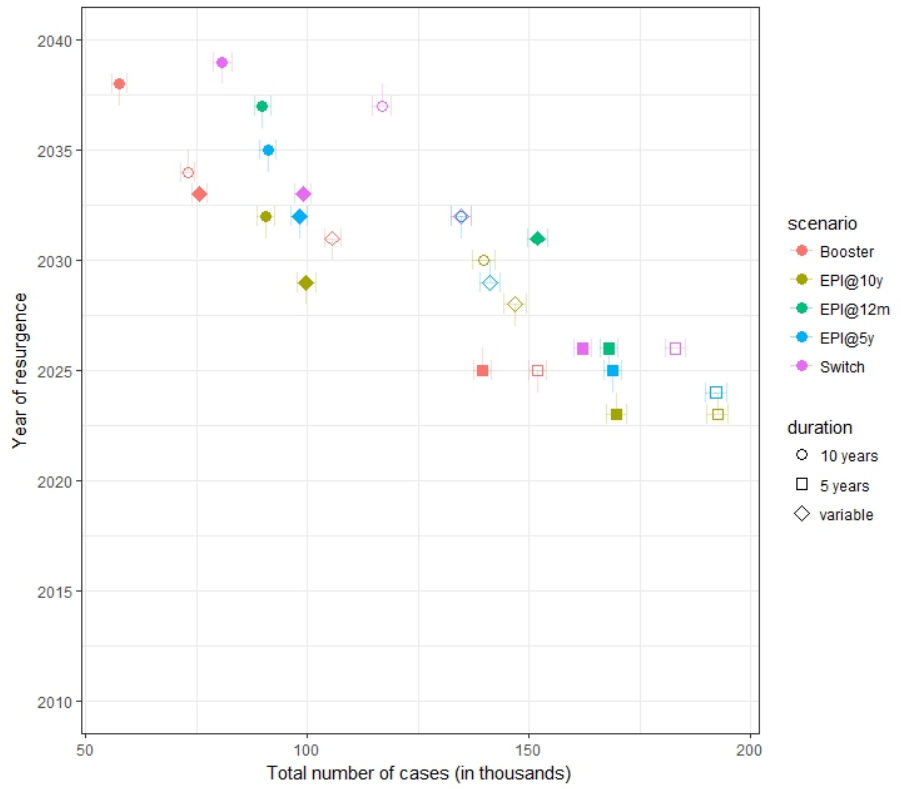


Fig. 6.5 Total number of cases plotted against the year of resurgence across all scenarios and all assumptions regarding duration of protection and coverage. Each strategy is represented with a different colour and each assumption about the duration of protection is represented with a different symbol shape. Symbols not filled with colour represent the low coverage scenario, that is 50%, while symbols filled with colour represent the high coverage, i.e 80%. Note that 20 years duration of protection is not shown. Error bars show the 95% confidence interval.

example, we can look at routine vaccination at either 12 months or 5 years when antibody response is short lived when children are targeted at the age of 12 months. In both cases, meningococcal cases start reappearing in 2028 but routine EPI at 5 years results in a total of 98,194 (95% CI: 96,303-100,086) cases while EPI at 12 months in 151,990 (95% CI: 149,829-154,151) cases.

6.4.4 Burden of disease

As one might expect, the scenario in which children who are routinely immunised at the age of 12 months and receive a booster dose on their fifth birthday, results in the

least number of cases across all different assumptions regarding the duration of antibody persistence.

Taking into consideration only the single-dose schedules, as can be seen in Figure 6.6, the model results suggest that if the duration of protection is assumed to be the same for everyone regardless of at what age an individual is targeted, routine immunisation at 12 months of age is no better than routine immunisation at older ages. There is considerable overlap in the results but strategy Switch is the strategy with the lowest average number of total cases predicted.

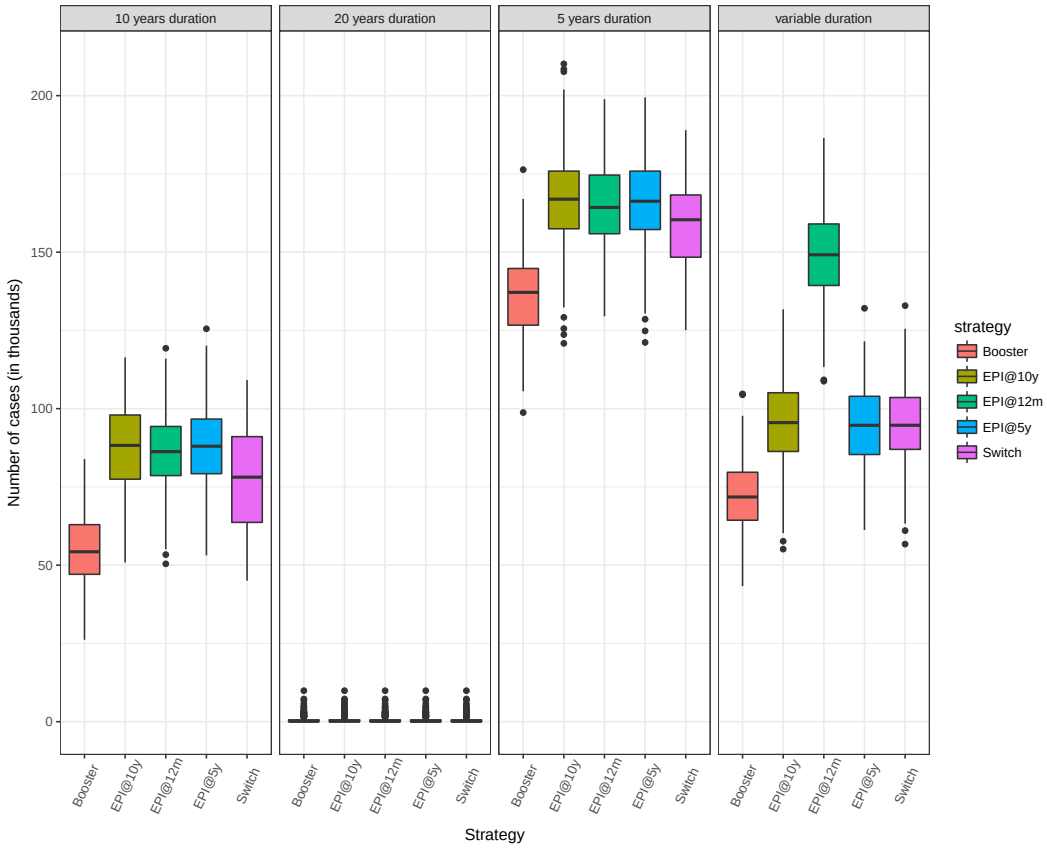


Fig. 6.6 Box plot showing the median, interquartile range, and full range of the predicted total number of cases for different immunisation strategies in the time period 2010-2060 from 200 simulation runs.

However, looking at the last panel on the right in Figure 6.6, assuming that vaccination of 1 year olds offers a shorter duration of protection compared to vaccination at older ages, the predicted number of cases is lower when children at the age of 5 or 10 are targeted for routine immunisation compared to children who are 12 months old. The

results for routine EPI at 5 years, 10 years and Switch strategy, all look very similar with no significant difference in the means (p-value=0.607). This is due to the mini catch-up campaign, which is present only in the Switch strategy, offering short lived protection as it targets young children with short lived antibody responses. The effect of the mini campaign on the results is explored in section 6.4.

Routine vaccination at older ages leaves a lot of children under the age of five unprotected and as a result, a large number of cases are predicted in that age group, as can be seen in Figure 6.7. Similarly, more cases in children older than five years are observed when routine EPI targets one year olds. This is due to waning of vaccine protection and it can be better seen in the two bottom panels of Figure 6.7, where the duration of vaccine induced protection is relatively short.

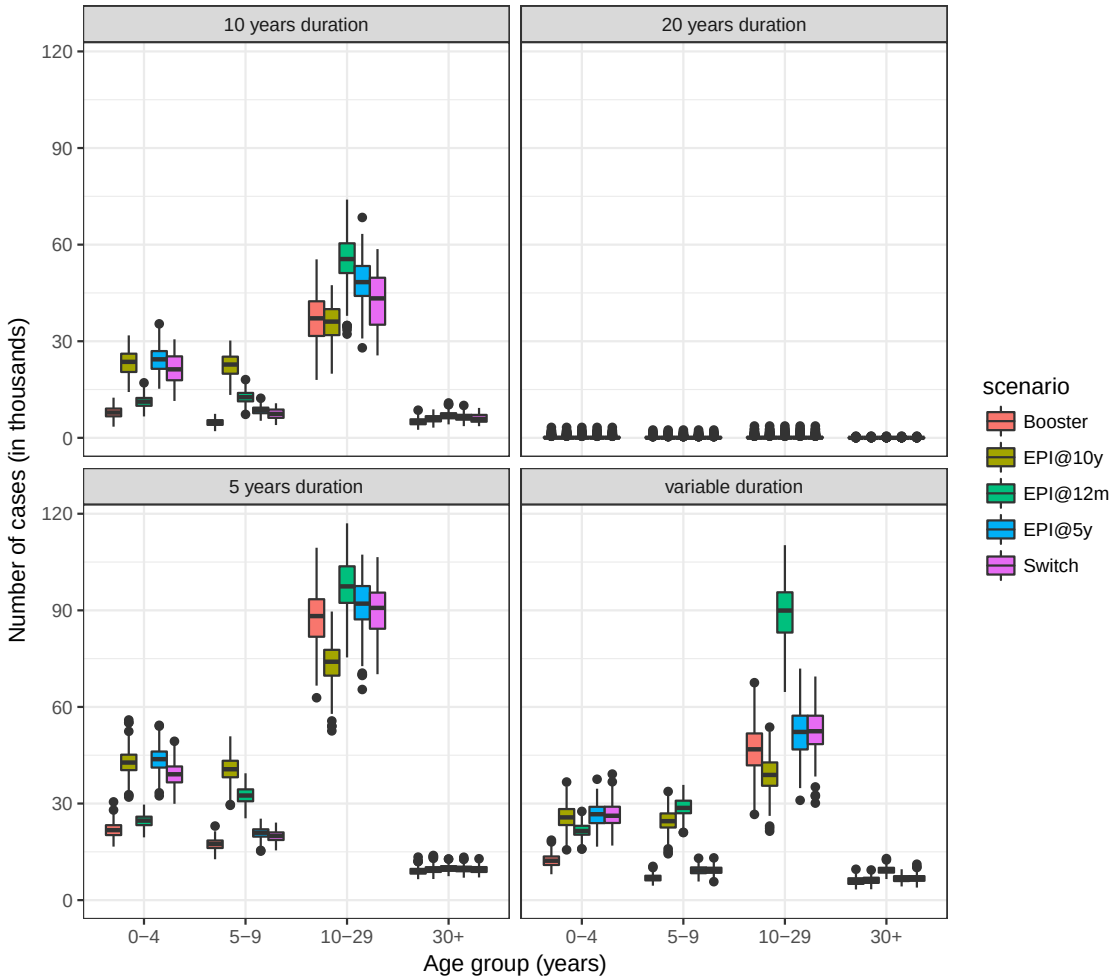


Fig. 6.7 Box plot showing the median, interquartile range, and full range of the total number of cases by age group from 200 simulation runs.

Vaccination programmes raise the average age of infection since young children are protected against disease. According to Figure 6.8, the strategy with the highest median age of infection and the lowest number of total cases is the 2-dose strategy which includes one dose at 12 months of age as well as a booster dose at a later age, when assuming the duration of vaccine induced immunity is 10 years for all ages.

Routine immunisation at ten years is associated with the lowest median age of infection due to the large number of unprotected children under the age of ten. It is clear from Figure 6.8 that the strategy with the highest median age of infection is the routine immunisation targeting children on their first birthday, with or without a booster dose when they turn 5 years of age.

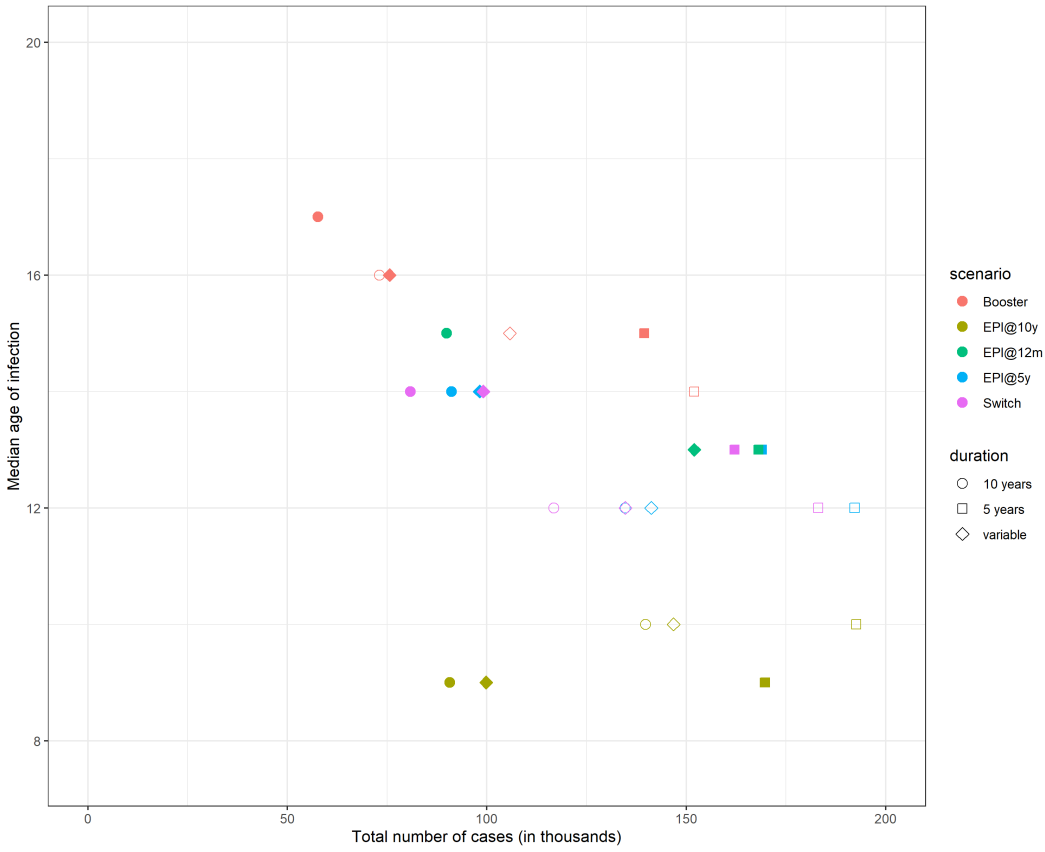


Fig. 6.8 Median age of disease plotted against the total number of cases across all scenarios and all assumptions regarding duration of protection and coverage. Each strategy is represented with a different colour and each assumption about the duration of protection is represented with a different symbol shape. Symbols not filled with colour represent the low coverage scenario, that is 50%, while symbols filled with colour represent the high coverage, i.e 80%.

6.4.5 Numbers needed to vaccinate

The initial mass campaign is common for all the scenarios I considered in this chapter. Assuming 100% coverage, which is consistent with the data, the number of doses given during the two phases of the campaign was 8,914,813. This was calculated by taking the number of people aged between 1 and 29 years in Chad in 2011. Note that vaccine wastage is not included in these calculations. When averaged across 200 simulation runs, the model predicts a total of 260,758 cases in the absence of any vaccination during the period 2011-2060. The number of doses together with the number of cases prevented for each scenario are given in Table 6.3. The number of doses given is not affected by the duration of vaccine protection but the number of cases predicted by the model is.

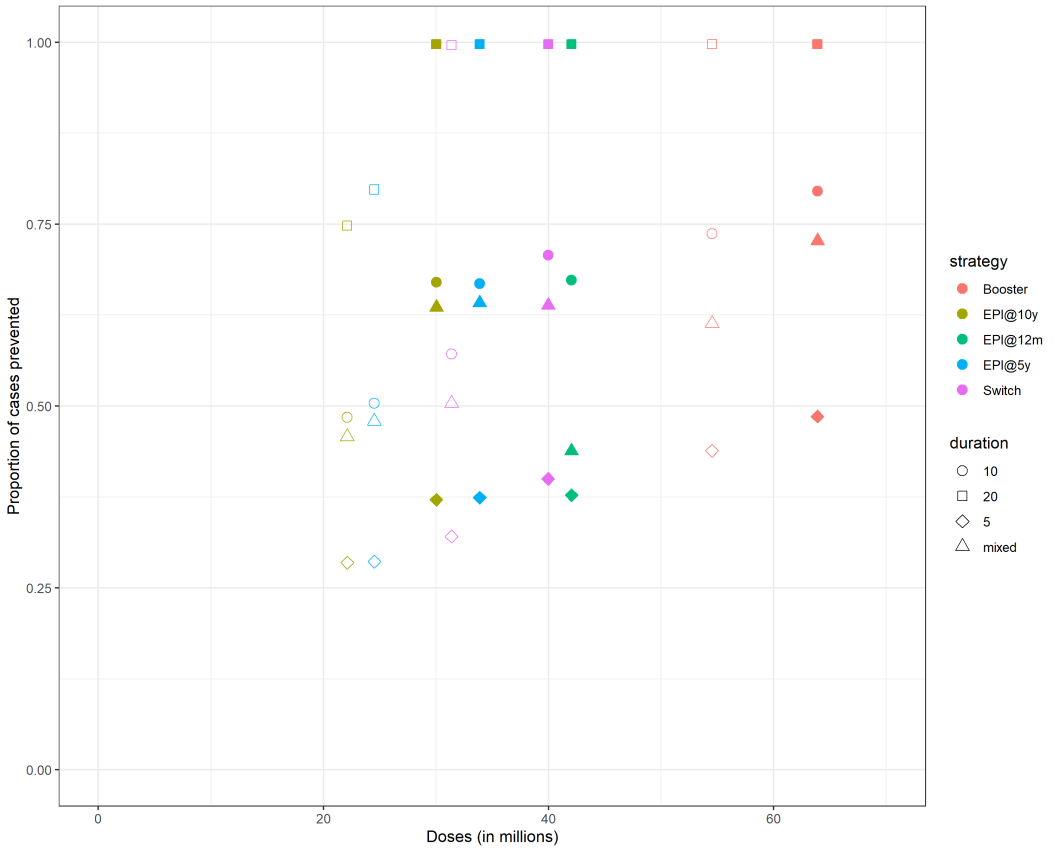


Fig. 6.9 Number of doses administered plotted against the proportion of cases prevented across all scenarios and all assumptions regarding duration of protection and coverage. Each strategy is represented with a different colour and each assumption about the duration of protection is represented with a different symbol shape. Symbols not filled with colour represent the low coverage scenario, that is 50%, while symbols filled with colour represent the high coverage, i.e 80%.

An efficient strategy would be the one that prevents the most cases of MenA using as few vaccine doses as possible.

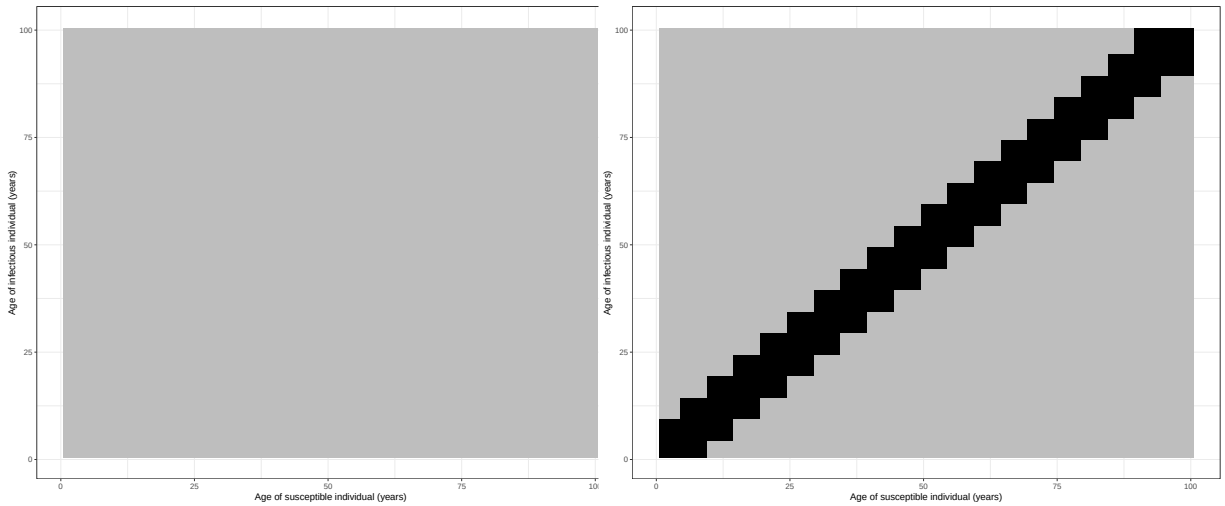
Assuming that MenAfriVac offers long protection that lasts for an average of 20 years, all strategies can be considered effective due to the small number of doses needed to prevent one case. On the other hand, if vaccine induced protection is five years for all ages, a large number of doses is required per case prevented while the total number of cases prevented is not the highest either.

Strategy	Coverage	Duration of protection	# of doses (in millions)	Cases	Cases prevented	NNV
EPI@12m	estimate	10 years	42.03	86,366	174,392	243 (240-247)
EPI@5y	80%	10 years	33.87	87,622	173,136	198 (195-200)
EPI@5y	50%	10 years	24.51	131,153	129,605	193 (189-198)
EPI@10y	80%	10 years	30.02	87,175	173,583	175 (172-177)
EPI@10y	50%	10 years	22.10	136,277	124,481	182 (178-186)
Switch	80% & estimate	10 years	39.96	77,344	183,414	220 (217-223)
Switch	50% & estimate	10 years	31.37	113,281	147,477	216 (212-219)
Booster	80% & estimate	10 years	63.88	54,092	206,666	311 (307-315)
Booster	50% & estimate	10 years	54.52	69,539	191,219	287 (284-291)
EPI@12m	estimate	5 years	42.03	164,537	96,221	450 (438-461)
EPI@5y	80%	5 years	33.87	165,412	95,346	367 (358-377)
EPI@5y	50%	5 years	24.51	188,672	72,086	364 (348-380)
EPI@10y	80%	5 years	30.02	166,190	94,568	329 (320-338)
EPI@10y	50%	5 years	22.10	189,069	71,688	331 (317-344)
Switch	80% & estimate	5 years	39.96	158,594	102,164	401 (392-409)
Switch	50% & estimate	5 years	31.37	179,533	81,225	403 (390-416)
Booster	80% & estimate	5 years	63.88	135,926	124,832	520 (510-530)
Booster	50% & estimate	5 years	54.52	148,420	112,338	498 (486-509)
EPI@12m	estimate	variable	42.03	148,459	112,299	382 (374-390)
EPI@5y	80%	variable	33.87	94,663	166,095	206 (203-209)
EPI@5y	50%	variable	24.51	137,679	123,079	204 (199-208)
EPI@10y	80%	variable	30.02	96,285	164,473	185 (182-188)
EPI@10y	50%	variable	22.10	143,272	117,486	193 (189-197)
Switch	80% & estimate	variable	39.96	95,564	165,194	245 (241-249)
Switch	50% & estimate	variable	31.37	131,166	129,592	247 (242-252)
Booster	80% & estimate	variable	63.88	72,097	188,661	341 (337-345)
Booster	50% & estimate	variable	54.52	102,207	158,551	348 (343-353)
EPI@12m	estimate	20 years	42.03	658	260,100	162 (160-164)
EPI@5y	80%	20 years	33.87	658	260,100	131 (130-132)
EPI@5y	50%	20 years	24.51	53,500	207,258	119 (118-121)
EPI@10y	80%	20 years	30.02	716	260,042	116 (115-117)
EPI@10y	50%	20 years	22.10	66,580	194,178	115 (113-116)
Switch	80% & estimate	20 years	39.96	658	260,100	155 (153-156)
Switch	50% & estimate	20 years	31.37	1,034	259,724	121 (120-123)
Booster	80% & estimate	20 years	63.88	658	260,100	247 (244-250)
Booster	50% & estimate	20 years	54.52	658	260,100	211 (209-213)

Table 6.3 Number of doses given, number of cases predicted and prevented and number of doses needed to prevent one case (NNV) under each immunisation strategy for the time period 2011-2060. Averaged across 200 simulation runs. 95% confidence intervals for NNV are provided in brackets. The word "estimate" under the coverage column represents the coverage estimate provided by Gavi which was described in Section 6.3.3.

6.5 Alternative contact matrices

So far throughout this thesis, the same contact matrix has been used in all the analyses and no sensitivity analysis on WAIFW matrices has been explored. Here, I attempt to explore the effects of using two alternative contact matrices on the model outputs. More specifically, I assume homogeneous mixing and assortative mixing, the structure of which can be seen in Figure 6.10. Homogeneous mixing assumes a constant transmission rate independent of age, while by assortative mixing I assume that individuals have higher contact rates between people of a similar age. More specifically, I assume that the contact rate between people with an age difference of five years is two times higher that the contact rate with the rest of the population.



(a) Homogeneous mixing (b) Assortative mixing

Fig. 6.10 Reperesentation of "who acquires infection from whom" (WAIFW) matrices for each mixing pattern. a) Homogeneous mixing. b) Assortative mixing. Black colour indicates twice as high contact rate between people with a five years age difference as with the rest of the population.

As an initial comparison of the consequences of using a different contact matrix, the model was run without seasonal forcing. For each WAIFW matrix, I ran the unforced model for 1,000 different values of the transmission parameter β drawn from a uniform distribution on the range (1,100) while keeping all other parameters fixed, and calculated the steady state (S^*,C^*,I^*,R^*). To ensure that the same effective values of β were used, as β ranged from 1 to 100, the steady state value of I^* was recorded. Then for each contact structure, the value of β was found for each the value of I^* was closest to the value of I^* calculated using the adapted WAIFW matrix. The value used for the homogeneous

mixing was $\beta = 18$ and for the assortative mixing was $\beta_1 = 13.5$ and $\beta_2 = 27$. The absolute differences in the values of the endemic steady state of the homogeneous and assortative mixing with the adapted matrix can be seen in Table 6.4.

	S^*	C^*	I^*	R^*
Homogeneous mixing	-0.0025	4.63e-05	1.707e-07	0.0025
Assortative mixing	-0.0013	1.817e-05	3.865e-07	0.0012

Table 6.4 Absolute amount by which the endemic fixed point of the unforced model with the adapted WAIFW matrix are smaller than those of the other mixing assumptions.

The model was subsequently run using the chosen transmission parameters for 200 values for the stochastic parameter for each mixing assumption using demographic data from Chad as discussed in section 6.2. For each run, the age-specific carriage prevalence during an epidemic peak was recorded. The results are shown in Figure 6.11.

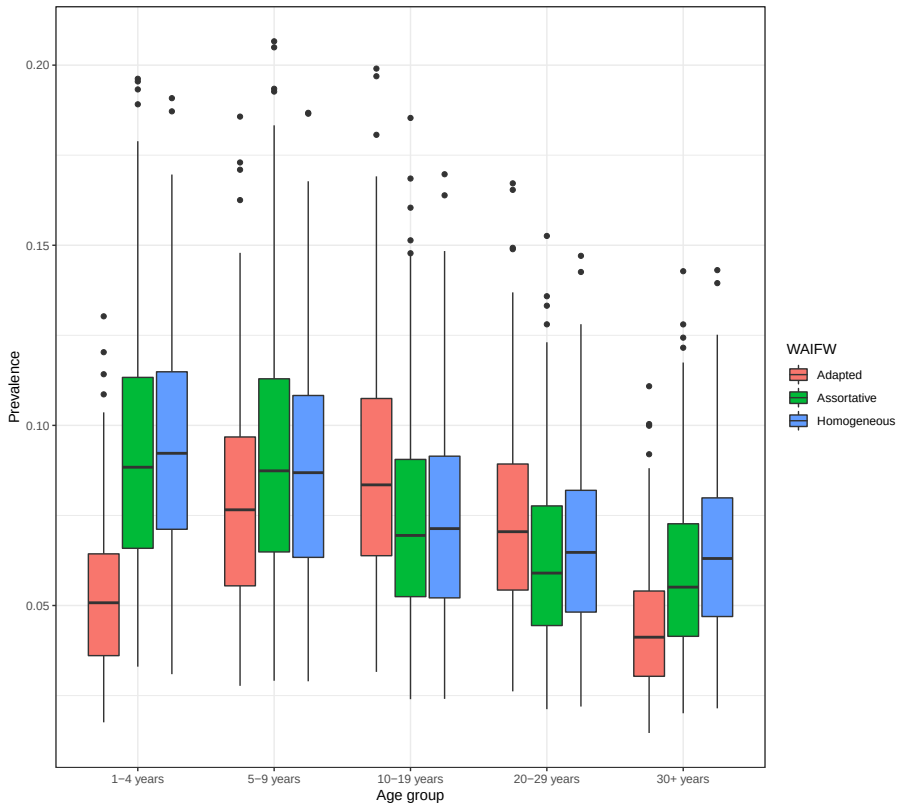


Fig. 6.11 Box plot showing the median, interquartile range and full range of the age-specific carriage prevalence during an epidemic peak for different mixing assumptions from 200 simulation runs.

For the homogeneous and assortative mixing pattern, carriage prevalence is highest among younger ages. This is in contrast to data suggesting that carriage prevalence peaks amongst individuals between 10 and 12 years of age, while it is not very high in children under the age of 5 years (Figure 3.3).

Time series of disease incidence with and without vaccination for each of the different contact patterns are seen in Figure 6.12. The results and the different predictions can be explained intuitively in the following way. The indirect effect of routine immunisation of one year old children is to raise the average age of infection. The adapted WAIFW matrix used so far in this thesis assumes that contact is higher among people aged between 15 and 30 years. Routine vaccination with an average duration of protection of 10 years means that susceptibility increases in the age group with the highest contacts thus leading to a stronger resurgence than would be predicted with either homogeneous or assortative mixing.

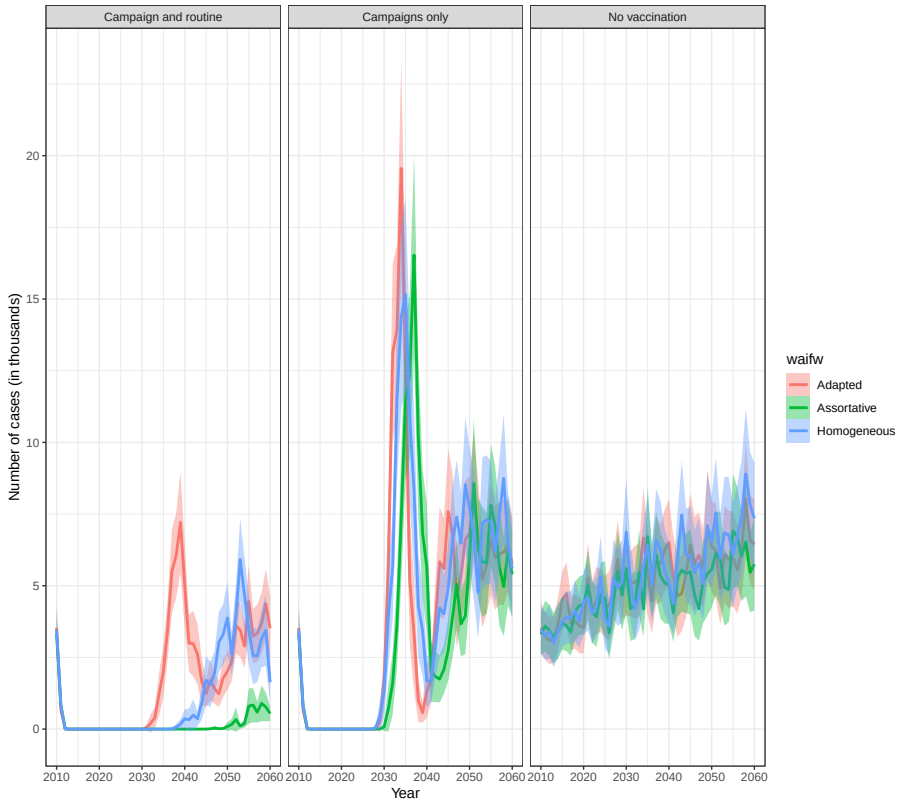


Fig. 6.12 Average disease incidence across the different vaccination scenarios and across the different assumptions regarding the contact pattern. Averaged across 200 simulation runs. Shaded areas represent the 95% confidence intervals. The campaign and routine scenario refers to the strategy EPI@12m.

6.6 Infant vs school children vaccination

The actual immunisation strategy used in Chad included two campaigns. One introductory mass campaign of 1 to 29 year olds completed in two phases in 2011-2012 and one catch-up campaign targeting children between the ages of 1 and 6 years at the start of routine EPI in 2017. The two campaigns offer very high levels of herd protection making it difficult to detect the direct effects of routine immunisation. To allow for comparison between immunising at different ages, I decided to consider a hypothetical scenario in which there are no campaigns, but instead, MenAfriVac is only routinely given to children aged 12 months, 5 years or 10 years.

To account for the fact that the vaccination of infants may provide a relatively short-term immune response compared to vaccination of older children, I investigated the effects of assuming five years of protection for EPI at 12 months.

I ran the model for a period of 50 years starting in 2010 using the demographic parameters of Chad and I considered the scenarios outlined in Table 6.5. The word "estimate" under the coverage column in Table 6.5 represents the coverage estimate provided by Gavi which was described in the methods.

Scenario	Start year	End year	Coverage	Duration of protection
EPI at 12 months	2010	2060	estimate	10 years
EPI at 12 months	2010	2060	80%	10 years
EPI at 12 months	2010	2060	estimate	5 years
EPI at 12 months	2010	2060	80%	5 years
EPI at 5 years	2010	2060	80%	10 years
EPI at 5 years	2010	2060	50%	10 years
EPI at 10 years	2010	2060	80%	10 years
EPI at 10 years	2010	2060	50%	10 years

Table 6.5 Complete set of scenarios explored assuming absence of any campaigns.

The results of the comparison of the strategies mentioned above can be seen in Figure 6.13. The numbers which can be seen above the boxplots indicate the values used for the coverage assumed and also the duration of vaccine induced protection. In the absence of an initial mass campaign, although there is considerable overlap between the results,

routine EPI at 10 years is the strategy which leads to the least number of cases, averaged across 200 simulation runs, when coverage is set at 80%.

Assuming that vaccination at 12 months offers protection for only five years, the light blue and light green boxplots in Figure 6.13 indicate that routine EPI at 5 years with only 50% coverage would lead to fewer total number of cases compared to routine EPI at 12 months. This translates to the first strategy being more efficient as it prevents more cases while using less vaccine doses.

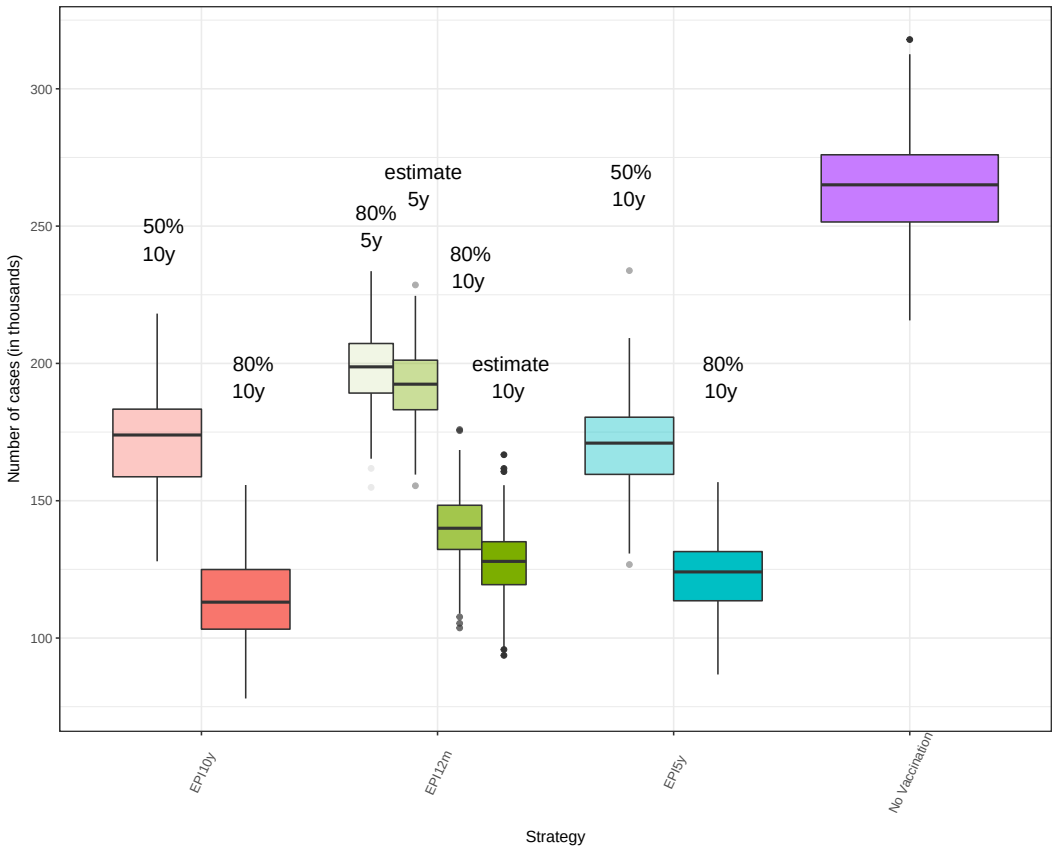


Fig. 6.13 Estimates of the average number of cases predicted in a scenario with no campaigns and routine EPI targeting different ages during the time period 2010-2060. Lighter shades indicate lower coverage. Exact values used for the coverage and duration of protection can be seen above each boxplot.

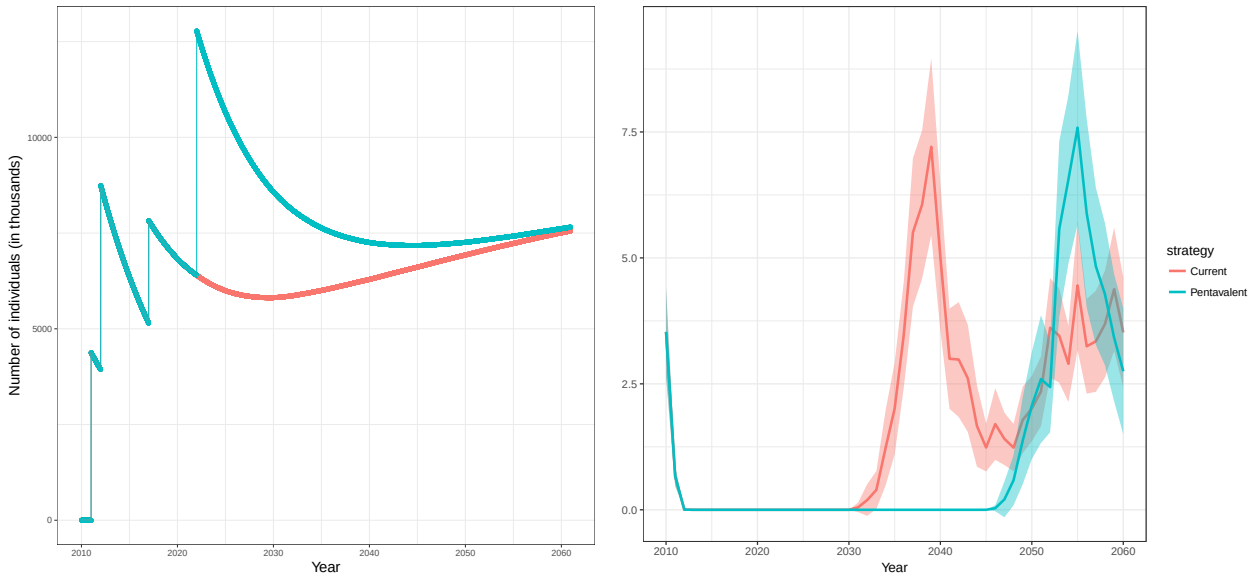
According to the computer simulations, routine EPI at older ages is more effective in reducing the overall number of cases predicted, however, this is done at the expense of pre-school children. More cases in the under five age group are predicted when routine immunisation is aimed at 5 or 10 year olds (Table 6.6).

Strategy	**Coverage (%)**	**Duration of protection (years)**	**Age of cases in years**				**Total**
			0-4	**5-9**	**10-29**	**30+**	
No vaccination	-	-	63.3	63.8	121.9	11.9	260.8
EPI at 12 months	estimate	10	17.3	21.1	77.4	8	123.9
EPI at 12 months	80	10	20.9	24.7	82.7	8.4	136.7
EPI at 12 months	estimate	5	28.5	39.7	109.7	10.3	188.1
EPI at 12 months	80	5	31.7	42	110.9	10.4	195
EPI at 5 years	80	10	34.6	12.6	64.8	7.5	119.5
EPI at 5 years	50	10	45	26.9	86	9.1	167
EPI at 10 years	80	10	30.7	30.4	43	6.7	110.8
EPI at 10 years	50	10	44.1	44.2	71.3	9	168.6

Table 6.6 Computer simulations of age-specific number of cases. Averaged across 200 simulation runs. The numbers of cases are reported in thousands.

6.7 Pentavalent vaccine

Although there has been more than a 99% decline in the number of confirmed *Neisseria meningitidis* A cases among countries that have been fully vaccinated with MenAfriVac, the disease incidence caused by non-A serogroup has increased with an incidence rate ratio of around 2.5 before and after vaccination [108]. In 2013, *Neisseria meningitidis* serogroup C started emerging in Nigeria [69] and is responsible for 8,000 cases and 500 deaths in Niger during the first semester of 2015 [115]. A new pentavalent vaccine targeting serogroups A, C, Y, W and X is currently in phase 1 clinical trial [116] and is expected to be available for use by 2022 [117]. Similarly to MenAfriVac, the new vaccine will be introduced to the population through a mass campaign followed by infant's routine immunisation. Work on the design of a new carriage study is ongoing and the age group targeted for the initial campaign is yet to be determined, although Gavi considered targeting 1 to 29 year olds or children aged between 5 and 14 years in its Vaccine Investment Strategy. However, it is worth exploring the potential benefits and effects on NmA of an additional mass campaign of 1 to 29 year olds taking place a decade after the first one.



(a) (b)

Fig. 6.14 Comparison of current strategy and vaccination with pentavalent.(a) Number of people in the vaccinated states over time. (b) Predicted average number of cases per year from 200 simulation runs. Shaded area identify the 95% confidence interval.

Computer simulations suggest that a mass campaign in 2022 with the new pentavalent vaccine will prevent a further 35,500 cases assuming that the current strategy continues unchanged until 2060 and children at the age of 12 months are routinely immunised. The greatest effect will be in children under the age of ten years, as the number of cases predicted in that age group will be halved, as shown in Table 6.7. The additional campaign will further delay the time to resurgence by 15 years (Figure 6.14b). Note that in Figure 6.14a the two lines initially overlap as vaccination with the pentavalent vaccine is assumed to take place in 2022.

Strategy	**0-4**	**5-9**	**10-29**	**30+**
No vaccination	63,334 (62,682 - 63,987)	63,760 (63,124-64,395)	121,815 (120,536-123,095)	11,849 (11,678-12,019)
Current strategy	11,280 (11,024-11,537)	12,695 (12,420-12,969)	55,441 (54,357-56,524)	6,950 (6,774-7,127)
Current strategy + Pentavalent vaccine	6,445 (6,171-6,718)	6,942 (6,663-7,221)	32,278 (31,166-33,391)	5,168 (4,949-5,387)

Table 6.7 Estimates of age-specific number of cases. Averaged across 200 simulation runs. 95% confidence interval around the mean is given in the brackets.

6.8 Discussion

The resurgence of meningococcal disease predicted by the model in the previous chapters has raised doubts about whether targeting infants for routine vaccination is the best way forward in reducing disease burden in the African meningitis belt. The idea that the immunisation of school-age children may result in better herd protection is supported by new studies [75, 76], indicating that protection lasts longer in individuals receiving MenAfriVac after the age of five years. I used the existing model to assess the impact of a set of new vaccination strategies and compared them to the actual strategy followed by the African countries since 2015.

Assuming that the duration of vaccine induced protection is shorter than 20 years, model results suggest that meningococcal disease cannot be eliminated within the first 50 years after initial vaccination by the current or the new strategies explored. The most extensive vaccination strategy (the booster strategy) leads to a 79.3% (95% CI: 78.7-79.8) overall reduction. On the contrary, provided that high antibody levels persist for an average of 20 years, all strategies, including the current, result in a possible elimination of MenA cases since there are no predicted cases until at least 2060.

Computer simulations indicate that in the absence of any immunisation campaigns, routine vaccination of 10 year olds would lead to the smallest average number of cases. However, including the campaigns, in the case of determining which strategy leads to the least number of cases, if we assume that the duration of protection is the same regardless of the age at vaccination, no single-dose strategy was superior to the rest, as there was considerable overlap in the results and there were no significant differences in their mean values. This is due to the mini catch-up campaign which is part of only the current strategy and not the other two (EPI at 5 or 10 years). The main difference in the results comparing the strategies is in the age distribution of cases. Reductions in the number of cases in one age group results in a rise of cases in another age group. Routine vaccination at 12 months offers better protection in young children, whereas vaccination at older ages reduces disease burden in adolescents and young adults. In the light of new data, if vaccine protection is short-lived in children under the age of 2 years, the model suggests that it would be wiser to change the target age of routine immunisation from 12 months to 5 years.

Based on the number needed to vaccinate (NNV), routine EPI at 10 years is consistently the most effective strategy across all different assumptions about the duration of vaccine protection. This is due to the small number of doses administered, calculated

based on the population demography of Chad. The strategy associated with the highest NNV is the addition of a booster dose. This is not surprising since the number of doses is almost double that of the rest of the strategies. NNV is widely used in the scientific literature. The nature of the disease (endemic, epidemic, high/low R_0) as well as the way NNV is calculated can produce biased results [118] and for this reason caution should be taken when interpreting results or comparing NNVs with other diseases in the scientific literature. However, the highest NNV value of 485 produced by the computer results if a booster dose of MenAfriVac is given to five-year-old children is far superior to NNV 2800-3700 estimated by Trotter *et al.* [119] when evaluating the response thresholds for reactive vaccination campaigns.

This is the first model to explore the potential benefits of targeting schoolchildren for routine immunisation with MenAfriVac. As in all mathematical models, there is a limitation in the uncertainty of the model structure and certain key model parameters. In this study, I expanded the model I first developed in 2015 and presented in Chapter 3 and used it to explore a range of new vaccination strategies. The results from this study were generated using demographic data from Chad, a country lying entirely in the meningitis belt and which suffered from epidemics every 8 to 12 years before the introduction of MenAfriVac in 2011. A number of key parameters, such as the transmission rate and the duration of natural immunity remain unknown and therefore I kept them the same allowing for a more direct comparison with the original study. As in all age-structured mathematical models, the mixing patterns are very important and especially when exploring vaccination strategies that target specific age groups. An exploration of alternative contact patterns showed that prediction of resurgence is sensitive to the WAIFW matrix assumed. The results assuming homogeneous and assortative mixing, however, are not realistic as they do not fit with known patterns of carriage. The carriage prevalence produced by the model using the adapted WAIFW matrix is consistent with contact studies in Africa, in which highest intensity of contacts is observed in 5-15 year-olds [120].

The overall conclusion of this study is that none of the strategies explored is superior in all respects. This is especially true when vaccine induced protection is the same for all ages. Vaccinating infants offers protection to young children and raises the median age of infection. However, the NNV to prevent one case is higher than the NNV to prevent one case when EPI targets 10 year-olds. Leaving children up to the age of ten unprotected, however, results in more cases in younger ages and less in older age groups. A possible

change in the current immunisation schedule would have to be based on the prioritisation of all the above factors.

Since the start of immunisation with MenAfriVac, there is an increased disease incidence caused by serogroups other than serogroup A. A new pentavalent vaccine is being developed and has completed phase I trials [116] with the expectation of licensure in the next three years [117]. I performed computer simulations as an initial attempt to estimate the potential benefits of an additional mass campaign of 1-29 year olds on NmA only. The results suggest that such a campaign would have a positive effect especially on the number of cases in the younger ages. In order to truly estimate the impact of introducing this new pentavalent vaccine in an already vaccinated population, a more robust study including a multi-serogroup model should be performed. This will involve a number of new unknown parameters and further increase the complexity of the model structure. Data on age-specific contact parameters would be desirable as well as data on age and serogroup specific case/carrier ratio. Yaesoubi *et al.* [86] developed a transmission dynamic model to investigate the cost-effectiveness of alternative vaccination strategies using the novel multivalent vaccine. All non-A serogroups were pooled into one group and the scenarios they explored included the replacement of MenAfriVac in the EPI and either the use of the novel vaccine in reactive campaigns or catch-up campaigns similar to the introduction of MenAfriVac. The age groups they considered for the campaigns were 1-29 years and 1-18 years. Yaesoubi *et al.* concluded that the inclusion of a catch-up campaign using the pentavalent vaccine is cost-efective and it will also contribute to a further reduction of meningococcal disease burden.

Despite the limitations of this study and the uncertainty surrounding the introduction of the pentavalent vaccine in the countries of the African meningitis belt, this analysis and conclusions drawn can be used in the future by policy makers to support a possible change in the current immunisation schedule. This change can either be the addition of a booster dose at a later age or simply the age of the primary dose. Additional work on the cost-effectiveness of such a change will also be essential before a definite conclusion can be reached.

Chapter 7

Discussion

7.1 Implications of my research

The plethora of options when designing a new public health intervention makes a mathematical model a powerful tool for policy makers. Its ability to make predictions about the progress of infectious diseases allows the evaluation of a wide range of scenarios that would be otherwise impractical to test in clinical trials. These predictions can be used to determine the best possible public health action.

Before the development of MenAfriVac, the approach for battling epidemics of meningitis in the African meningitis belt was based on the use of polysaccharide vaccines in reactive campaigns. The success of a reactive campaign however, depends on the early detection of an emerging epidemic as well as the rapid arrival of the vaccine to the affected areas. This tends to make reactive responses very inefficient. A conjugate vaccine, like MenAfriVac, could be used in a preventive campaign more efficiently and with greater success. My research was motivated by the challenges of investigating potential long-term immunisation strategies with the new conjugate vaccine, MenAfriVac to achieve its maximum potential.

Building on previous work [82], I developed an age-structured transmission dynamic model able to describe the epidemiology of NmA in countries of the African meningitis belt. I considered several different immunisation strategies including the use of the vaccine solely in an one-off introductory mass campaign of 1 to 29 year olds and showed that the absence of any long-term vaccination plan could lead to a catastrophic resurgence of disease.

This result provides the main public health conclusion of this thesis, which is that failure to introduce MenAfriVac into the countries' routine immunisation schedule could

have disastrous consequences. The Expanded Programme on Immunisation (EPI) in Africa has been continuously improving since its initiation around 40 years ago [121] and the addition of MenAfriVac to the schedule can only strengthen the current infrastructure and save even more lives in the high risk areas, as the demand for MenAfriVac may also drive up measles vaccination coverage. Additionally, MenAfriVac gives an excellent tetanus boost [68]. Despite the model not being systematically fitted to data, its predictions were well perceived by WHO's experts. The results of the model presented in Chapter 3, accompanied by a cost-of-illness study [96], formed the basis of WHO's recommendation concerning the use of MenAfriVac in the African meningitis belt. It was recommended that countries should introduce the vaccine into routine childhood immunisation schedule together with a mini catch-up campaign after completing the initial campaign of 1 to 29 year olds. Up to the time of writing, the majority of the countries have adopted the recommended strategy.

Continuous monitoring of the situation and updating model parameters as new data become available may lead to possible future changes in the vaccination strategy, especially if vaccine-induced immunity is proved to be short-lived for children vaccinated before the age of two years. The work in Chapter 6 highlighted the effect of the assumptions regarding the duration of vaccine protection on the model-derived predictions. Assuming that duration of immunity provided by MenAfriVac varies depending on the age at vaccination, I showed the potential benefits of either targeting older children for routine vaccination or adding a booster dose to the current schedule. The caveat of adding a booster dose is that it will be a more costly intervention, however, it may be the optimal way to maintain longer-term protection levels.

The use of a model, however, is not limited to the guidance of a new intervention or the aid with the planning for the response to an emerging disease. The work for VIMC in Chapter 5 showed how a model can be used to estimate disease burden and assist funders in monitoring the progress of meeting their set goals. I was asked to provide estimates on vaccine impact for each of the 26 countries of the African meningitis belt. These estimates, generated every other year, are used by Gavi and the Bill and Melinda Gates Foundation to support decision making on future investments as well as to evaluate their existing vaccination programmes. The number of cases due to meningococcal meningitis account for only a small fraction of the total number of cases caused by other more common vaccine-preventable diseases, like measles, in the African nations. The estimates generated within VIMC are used in cost-of-illness studies which provide information

about the efficiency of a vaccination policy. These estimates are also used to monitor Gavi's progress towards the Decades of Vaccine (DoV) targets.

The VIMC consists of modellers as well as public health representatives. This strengthens the connection between the two fields which is vital in communicating science in coherent ways. Accurate description of how the model works and its limitations is essential to avoid possible confusion about how data should be used. The national coverage estimates provided by Gavi were adjusted to account for the fact that only a proportion of a country's population is at risk. The assumptions behind these adjustments are not made clear which leads to the next key conclusion from my thesis - the importance of reproducibility in data science.

The ongoing reproducibility crisis (or replication crisis) the scientific community is facing is of great concern. Science moves forward by building on existing work by others and corroboration. However, progress is often obstructed by building on questionable methods and results. Irreproducible results can arise from either intentional misconduct [122] or from inaccurate reporting like in the case of Tartof *et al.* [84]. Specifically for epidemic models, transparency in reporting the methods and data used is of key importance to ensure that the results can be replicated by an independent researcher. Journals have been working on ways to promote transparency by introducing more rigorous checklists addressing areas of reporting [123].

The work presented in Chapter 4 highlighted the importance of the authors sharing their computer code when questions regarding the validity of the results arise. Sharing the code however does not imply that all issues are immediately resolved. Reproducing the findings of a published paper can be a very time-consuming process [123]. Researchers may use different programming languages or a specific software may be essential to run a code on a computer. Further, researchers are not software engineers and this means that their code may not be perfect and a lot of time is needed to clean it. This is one possible explanation as to why few researchers publish their codes together with the papers.

7.2 Limitations and future directions

My models only consider carriage and disease solely due to *Neisseria meningitidis* serogroup A. I assume that cycles of NmA are independent of the other serogroups, i.e. in this model there is no potential for serogroup replacement. The protection of people against the dominant type (selective nature of vaccine protection), allows serogroups with previously low prevalence to grow rapidly [124] and lead to a possible strain replacement

[125]. This phenomenon is known as *vaccine-induced pathogen strain replacement* [126]. After the successful vaccination with MenAfriVac, prevalence of NmA dropped while there have been outbreaks caused by serogroups W and C [69, 70] creating a new public health problem. However, genetic epidemiology studies guided WHO to state that MenAfriVac was unlikely to have driven replacement with group C [127].

Evaluating a totally new vaccine can be challenging. Although my models are single-strain models focusing only on NmA, insights gained into the potential impact of vaccination aimed at different ages can be used to guide the design of new carriage studies. Results from these studies can then be fed into a more complex multi-strain model, more suitable for the evaluation of impact of the novel polyvalent vaccine. Van Effelterre *et al.* [128] developed a multi-strain model to reproduce serogroup specific changes in invasive pneumococcal disease since vaccination with the 7-valent pneumococcal conjugate vaccine (PCV7). This model focuses only on <2 year olds and therefore does not account for herd immunity. Previous models describing the impact of vaccination on *Neisseria meningitidis*, including the most recent model by Yaesoubi *et al.* [86], have pooled all serogroups into two or three groups [80, 129]. However, this aggregation may have an impact on the predictions regarding the effectiveness of vaccination [130]. Thus, although my model is not fully comprehensive of *Neisseria meningitidis* dynamics, it is sufficient to answer the research question posed.

The work presented in Chapter 5 is based on the stratification of the countries into high-medium-low incidence countries. This classification was deemed necessary as there are insufficiently high quality surveillance datasets over a long period of time to allow the parameterisation of the model on a country-to-country basis. This is the best we can do with current data sources. As a result, key parameters such as the transmission rate and duration of colonisation are difficult to obtain estimates for. With incidence data limited to annual observations, direct estimation of model parameters is complicated. Other approaches have been published, e.g. Yeasoubi *et al.* [86] developed a model disaggregated by districts and used weekly incidence data on a district level. This district level data was not available to me and I was addressing different question, so this was less appropriate.

My initial attempts at model fitting have been made using two long incidence time series from Burkina Faso and Chad. No results from these attempts have been formally incorporated into the model as the model fits appeared to have identifiability issues. These issues could be ameliorated by an estimate of the R_0 by re-examining all data

available. This estimate together with a more recent carriage prevalence curve could be incorporated into a formal model fitting process.

The results from Chapter 5 highlighted the importance of demography and contact patterns. Shifts in demography were shown to have an effect on disease incidence even in the absence of vaccination. This finding is consistent with the results from a study investigating the effects of demographic changes in disease transmission which showed that lower fertility levels lead to an increase in the average age at infection [131]. I made assumptions about the contact patterns in my models. Using empirical data on age-structured contact patterns would test the validity of my findings. To my knowledge, none is yet available for the African meningitis belt countries. If further studies to be conducted, the type of contact measured should be relevant to NmA, that is, close and prolonged contact is necessary to transmit the bacteria from one person to the other.

An area of improvement to my work for the VIMC is the development of sub-national models for countries that are only partially at risk. Countries like Nigeria and Cameroon for example, introduce MenAfriVac through mass immunisation campaigns into part of the country while they are planning to implement nationwide routine vaccination. This heterogeneity in vaccine implementation should be captured in the model. Models at a finer scale have been motivated by the need to support decision making at a province level [132] or to investigate implications of spatial heterogeneity in vaccination coverage [133]. Any spatial model aiming to investigate the impact of sub-national campaigns with either MenAfriVac on the new pentavalent vaccine should allow for connectivity between regions and/or other countries.

Genomic studies have illustrated the global spread of different strains of meningococci [134, 135]. Serogroup W strain causing epidemics in sub-Saharan Africa since 2001 has been shown to be closely related to a Hajj-associated outbreak of MenW disease in 2000. This Hajj strain has subsequently been detected in isolates from France and Turkey. A distinct from the Hajj outbreak serogroup W strain is currently endemic in South America, England and Wales [134]. International human movements are therefore important in meningococcal epidemiology. In my model I have not allowed for any migration or sort term travel from one country to the other and have treated each country as a closed population. The impact of migration could be explored with the addition of an external force of infection, such as the one used by Tartof *et al.* in their model [84]. Disease is transmitted from asymptotic carriers and results from studies estimating overall carriage prevalence in the African nations vary in the range 3.5%-35% [18]. This wide range in carriage prevalence estimates makes it not possible to accurately quantify an external

force of infection. The key reason for not using any external force of infection in the model is that the vast majority of cases of *Neisseria meningitidis* serogroup A are concentrated in the countries of the African meningitis belt and only rare sporadic cases occur in the rest of the world. All the high incidence African countries implement vaccination with MenAfriVac in a period of 5 years resulting in the eradication of serogroup A cases from vaccinated populations. I assumed therefore that the potential transmission from outside of the country is negligible and was not included in the model in the form of a constant external force of infection.

7.3 Conclusion

Mathematical models are extremely valuable for the evaluation of current and future vaccine interventions. This thesis demonstrated two different ways a mathematical model can be used to support decision making. I developed a model to advise on future vaccination plans with MenAfriVac by evaluating the impact of a range of possible immunisation strategies and applied it to estimate disease burden across all the countries of the African meningitis belt. Mathematical models should be integral to informing policy makers for the development, investment and implementation of any new vaccine.

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Appendix A

The derivation of the model has three parts. Firstly, the equation of age dependent population growth, the Lotka-McKendrick model, is defined. Secondly, expressions for the sizes of each age group are derived. Finally, age groups are incorporated into the model.

A.1 Age-dependent population growth

Let $U(z,t)$ be a function describing the distribution of ages in a population, so that at time t the number of people whose age z is in the interval $[z_1, z_2]$ is given by

$$\int_{z_1}^{z_2} U(z,t)dz, \tag{A.1}$$

and so the total population is

$$\int_{0}^{\infty} U(z,t)dz. \tag{A.2}$$

Let the age-specific mortality rate be denoted by $d(z) > 0$. Then the dynamics of the age distribution are described by the Lotka-McKendrick model [136], also known as the McKendrick-von Foerster model [90],

$$\frac{dU}{dt} = \frac{\partial U}{\partial t} + \frac{\partial U}{\partial z} = -d(z)U(z,t). \tag{A.3}$$

The boundary condition of the Lotka-McKendrick model A.3, $U(0,t)$, is the birth rate $B(t)$, given by

$$B(t) = U(0,t) = \int_{0}^{\infty} f(z)U(z,t)dz \tag{A.4}$$

where $f(z)$ is the age-specific fertility rate.

A.2 Initial sizes of age groups

In order to allow for a comparison with actual data, it is more convenient to use an alternative representation of the age-structured model, where rather than consider age in population as a continuous variable, the population is divided into n age classes, with the j^{th} class covering the age range $[z_{j-1}, z_j]$ for $0 = z_0 < z_1 < z_2 ... < z_{n-1} < z_n = \infty$. It is assumed that all individuals in the age range $[z_{j-1}, z_j]$ have the same death and fertility rates as someone with age z_j, so for $z \in [z_{j-1}, z_j], d(z) = d(z_j)$ and $f(z) = f(z_j)$. Denote the size of the j_{th} age group at time t as $N_j(t)$, and at time 0 as P_j $(= N_j(0))$, and let the initial age distribution of the population be $A(z)$. Then

$$P_j = \int_{z_{j-1}}^{z_j} A(z)dz. \tag{A.5}$$

As previously discussed, the age distribution is assumed to be stationary with the total population increasing at a rate q, that is,

$$U(z,t) = e^{qt}A(z). \tag{A.6}$$

The size of the j^{th} age group at time t is thus

$$N_j(t) = \int_{z_{j-1}}^{z} U(z,t)dz = e^{qt}\int_{z_{j-1}}^{z_j} A(z)dz = e^{qt}P_j, \tag{A.7}$$

so each age group is growing, but the proportion of the total population that is in each age group remains constant.

To define the initial population sizes P_j, substitute the expression for the time-dependent age distribution (A.6) into the McKendrick-von Foerster equation (A.5):

$$e^{qt}\frac{dA}{dz} + qe^{qt}A(z) = -d(z)e^{qt}A(z) \;\Rightarrow\; \frac{dA}{dz} = A(z)[-q - d(z)]. \tag{A.8}$$

Since $d(z)$ is constant in the interval $[z_{j-1}, z_j]$, integrating Equation (A.8) on that interval gives, for $z \in [z_{j-1}, z_j]$,

$$A(z) = C\exp(-z(d_j + q)) \tag{A.9}$$

where C is a constant that is found by evaluating $A(z)$ at $z = z_{j-1}$:

$$A(z_{j-1}) = C\exp[-z_{j-1}(d_j + q)] \;\Rightarrow\; C = A(z_{j-1})\exp[z_{j-1}(d_j + q)]. \tag{A.10}$$

Thus the relative population densities at ages z and z_{j-1} are

$$A(z) = A(z_{j-1}) \exp[-(d_j + q)(z - z_{j-1})]. \tag{A.11}$$

By integrating this on $[z_{j-1}, z_j]$ again, the expression for the initial size of the j^{th} age group can be found:

$$\begin{aligned}
P_j &= \int_{z_{j-1}}^{z_j} A(z)dz && \text{(A.12)}\\
&= \int_{z_{j-1}}^{z_j} A(z_{j-1}) \exp[-(d_j + q)(z - z_{j-1})]dz && \text{(A.13)}\\
&= \left[\frac{A(z_{j-1})}{-(d_j + q)} \exp[-(d_j + q)(z - z_{j-1})]\right]_{z_{j-1}}^{z_j} && \text{(A.14)}\\
&= \frac{A(z_{j-1})}{-(d_j + q)} \exp[-(d_j + q)(z_j - z_{j-1})] + \frac{A(z_{j-1})}{d_j + q} && \text{(A.15)}\\
&= \frac{A(z_{j-1})}{d_j + q} \left[1 - \exp[-(d_j + q)(z_j - z_{j-1})]\right]. && \text{(A.16)}
\end{aligned}$$

Notice that, from (A.11), it follows that

$$A(z_{j-1}) - A(z_j) = A(z_{j-1})(1 - \exp[-(d_j + q)(z_j - z_{j-1})]), \tag{A.17}$$

which can now be written as

$$A(z_{j-1}) - A(z_j) = P_j(d_j + q). \tag{A.18}$$

Next, the rate of progression between age groups is defined. Let the constants K_j be the rates at which people move from age group j to the age group $j + 1$. This is given by the proportion of the people in the age group who have age j. If the age distribution were flat, this would be given by $1/(z_j - z_{j-1})$. However, this is not the case here, so a more general form must be used:

$$K_j = \frac{A(z_j)}{\int_{z_{j-1}}^{z_j} A(z_j)dz} = \frac{A(z_j)}{P_j}. \tag{A.19}$$

By substituting the expression for P_j from (A.16) and $A(z_j)$ from (A.11) evaluated at z_j, this is equivalent to

$$K_j = \frac{A(z_j)}{P_j} \tag{A.20}$$

$$= \frac{A(z_j)}{A(z_{j-1})\left[1 - \exp[-(d_j+q)(z_j - z_{j-1})]\right]/(d_j+q)} \tag{A.21}$$

$$= \frac{A(z_j)\exp[-(d_j+q)(z_j - z_{j-1})]}{A(z_{j-1})\left[1 - \exp[-(d_j+q)(z_j - z_{j-1})]\right]/(d_j+q)} \tag{A.22}$$

$$= \frac{(d_j+q)\exp[-(d_j+q)(z_j - z_{j-1})]}{1 - \exp[-(d_j+q)(z_j - z_{j-1})]} \tag{A.23}$$

$$= \frac{(d_j+q)}{\exp[(d_j+q)(z_j - z_{j-1})] - 1}. \tag{A.24}$$

A.3 SCIRS model with continuous age distribution

The age-dependent form of the SCIR model is given by

$$\left(\frac{\partial}{\partial z} + \frac{\partial}{\partial t}\right) s = \phi r - (\lambda(z,t) + d(z))s, \tag{A.25}$$

$$\left(\frac{\partial}{\partial z} + \frac{\partial}{\partial t}\right) c = \lambda s - (a + \alpha + d(z))c, \tag{A.26}$$

$$\left(\frac{\partial}{\partial z} + \frac{\partial}{\partial t}\right) i = ac - (\rho + d(z))i, \tag{A.27}$$

$$\left(\frac{\partial}{\partial z} + \frac{\partial}{\partial t}\right) r = \rho i + \alpha c - (\phi + d(z))r, \tag{A.28}$$

where $\lambda(z,t)$ is the age-specific force of infection, $d(z)$ is the age-specific mortality rate, and s, r, c and i be, respectively, the density of people who are susceptible, immune, asymptomatic carriers, or have meningitis. The birth rate is described by the boundary conditions, which depend on the age-specific fertility rate $f(z)$:

$$s(0,t) = \int_0^\infty f(z)[s(z,t) + c(z,t) + i(z,t) + r(z,t)]dz, \tag{A.29}$$

$$c(0,t) = i(0,t) = r(0,t) = 0. \tag{A.30}$$

A.4 SCIRS model with discrete age groups

Finally, the methodology explained in Section A.2 can be used to derive the age-group representation of model A.25 - A.28. The number of susceptibles in the j^{th} age class $[z_{j-1}, z_j]$, is given by

$$s_j(t) = \int_{z_{j-1}}^{z_j} s(z,t)dz, \tag{A.31}$$

and likewise for $c_j(t), i_j(t)$ and $r_j(t)$. Analogously to the definition of K_j in A.19, $\frac{s(z_j,t)}{s_j} = K_j, \frac{c(z_j,t)}{c_j} = K_j$ etc., since people all age in the same way regardless of their infection status.

Consider initially the equation A.25, for $2 \leq j \leq n$. Differentiation of A.31 and rearrangement using A.25-A.28 gives

$$\begin{aligned}
\frac{d}{dt}s_j(t) &= \int_{z_{j-1}}^{z_j} \frac{\partial s(z,t)}{\partial t}dz && \text{(A.32)}\\
&= \int_{z_{j-1}}^{z_j} [\phi r(z,t) - \lambda_j s(z,t) - d(z)s(z,t)]dz - \int_{z_{j-1}}^{z_j} \frac{\partial s(z,t)}{\partial z}dz && \text{(A.33)}\\
&= \phi r_j(t) - (\lambda_j + d_j)s_j(t) - s(z_j,t) + s(z_{j-1},t) && \text{(A.34)}\\
&= \phi r_j(t) - (\lambda_j + d_j + K_j)s_j(t) + K_{j-1}s_{j-1}(t). && \text{(A.35)}
\end{aligned}$$

Since the age-distribution is stationary and the number of people in each age group is growing exponentially, it is more straightforward to work with not the absolute number of people that is in each compartment, s_j, c_j, etc., but rather the proportion of the age group that is in each compartment, S_j, C_j, etc. This is done by normalising the age-dependent compartments as proportions of their respective age groups, $N_j(t) = e^{qt}P_j$:

$$S_j(t) = \frac{s_j(t)}{e^{qt}P_j}, C_j(t) = \frac{c_j(t)}{e^{qt}P_j}, I_j(t) = \frac{i_j(t)}{e^{qt}P_j}, R_j(t) = \frac{r_j(t)}{e^{qt}Pj}. \tag{A.36}$$

Using these definitions and A.32 - A.35,

$$\begin{aligned}
\frac{dS_j}{dt} &= \frac{d}{dt}\left(\frac{1}{e^{qt}P_j}s_j(t)\right) && \text{(A.37)}\\
&= \frac{1}{e^{qt}P_j}\frac{ds_j(t)}{dt} - \frac{q}{e^{qt}P_j}s_j(t) && \text{(A.38)}
\end{aligned}$$

$$= \frac{1}{e^{qt}P_j}\left[\frac{ds_j(t)}{dt} - qs_j(t)\right] \tag{A.39}$$

$$= \frac{1}{e^{qt}P_j}[\phi r_j(t) - (\lambda_j + d_j + K_j)s_j(t) + K_{j-1}s_{j-1}(t) - qs_j(t)] \tag{A.40}$$

$$= \phi R_j(t) + K_{j-1}S_{j-1}(t) - (\lambda_j + d_j + K_j + q)S_j(t). \tag{A.41}$$

This is valid for $2 \leq j \leq n$. However, S_0 and K_0 are currently undefined. People enter S_1 by being born rather than tranferring from younger age groups. So in this case

$$\frac{d}{dt}s_1(t) = \int_{z_0}^{z_1}\frac{\partial s(z,t)}{\partial z}dz = s(z_1,t) - s(z_0,t) \tag{A.42}$$

$$= K_1 s_1 - s(0,t), \tag{A.43}$$

where $s(0,t)$ is the birth term $A(0)$. An alternative expression for $A(0)$ can be derived from A.18,

$$A(z_1) - A(z_0) = -P_1(d_1 + q) \tag{A.44}$$

$$A(z_0) = A(z_1) + P_1(d_1 + q) \tag{A.45}$$

$$A(0) = K_1P_1 + P_1(d_1 + q) \tag{A.46}$$

$$= (K_1 + d_1 + q)P1, \tag{A.47}$$

so the birth rate is $(K_1 + d_1 + q)P1$, therefore

$$\frac{dS_1}{dt} = \phi R_1(t) + (K_1 + d_1 + q)P_1 - (\lambda_1 + d_1 + K_1 + q)S_1(t). \tag{A.48}$$

The expression for $\frac{dC_j}{dt}$, $\frac{dI_j}{dt}$, and $\frac{dR_j}{dt}$ are derived in a similar way.

The force of infection for the j^{th} age group is given by

$$\lambda_j = \sum_{k=1}^{n}\beta(z_j, z_k)(I_k + C_k) \tag{A.49}$$

where $\beta(z_j, z_k)$ is the contact rate between people in the j^{th} and k^{th} age classes.

The complete age structured SCIRS model is therefore given by the following system of coupled ordinary differential equations:

$$\frac{dS_1}{dt} = (K_1 + d_1 + q)P1 + \phi R_1 - (\lambda_1 + d_1 + K_1 + q)S1 \tag{A.50}$$
$$\frac{dS_j}{dt} = K_{j-1}S_{j-1} + \phi R_j - (\lambda_j + d_j + K_j + q)S_j,\ 2 \leq j \leq n \tag{A.51}$$
$$\frac{dC_1}{dt} = \lambda_1 S_1 - (a + \alpha + d_1 + q + K_1)C_1 \tag{A.52}$$
$$\frac{dC_j}{dt} = K_{j-1}C_{j-1} + \lambda_j S_j - (a + \alpha + d_j + q + K_j)C_j,\ 2 \leq j \leq n \tag{A.53}$$
$$\frac{dI_1}{dt} = aC_1 - (\rho + d_1 + q + K_1)I_1 \tag{A.54}$$
$$\frac{dI_j}{dt} = K_{j-1}I_{j-1} + aC_j - (\rho + d_j + q + K_j)I_j,\ 2 \leq j \leq n \tag{A.55}$$
$$\frac{dR_1}{dt} = \rho I_1 + \alpha C_1 - (\phi + d_1 + q + K_1)R_1 \tag{A.56}$$
$$\frac{dR_j}{dt} = K_{j-1}R_{j-1} + \rho I_j + \alpha C_j - (\phi + d_j + q + K_j)R_j,\ 2 \leq j \leq n \tag{A.57}$$

where $K_j = 0$.

A.5 Calculation of the age distribution

The age-dependent mortality rates d_j and the population growth rate q can be estimated directly from data. Using these, the transfer rates K_j can be calculated from Equation A.24:

$$K_j = \frac{(d_j + q)}{\exp[(d_j + q)(z_j - z_{j-1})] - 1}. \tag{A.58}$$

To calculate the initial sizes of the age groups, P_j, recall from A.18 that

$$A(z_{j-1}) - A(z) = P_j(d_j + q). \tag{A.59}$$

Then, using the definition of K_j from A.19,

$$K_{j-1}P_{j-1} - K_j P_j = P_j(d_j + q) \tag{A.60}$$
$$P_j(K_j + d_j + q) = K_{j-1}P_{j-1} \tag{A.61}$$
$$P_j = \frac{K_{j-1}P_{j-1}}{K_j + d_j + q},\ for\ j \geq 2. \tag{A.62}$$

Iterating this from $j = 2$ gives

$$P_j = \frac{K_{j-1}K_{j-2}...K_1P_1}{(K_j + d_j + q)...(K_2 + d_2 + q)}. \tag{A.63}$$

The values of P_j can be found by choosing an arbitrary P_1, calculating the other P_j from A.62 and then normalising each by their sum. Note that since S_j, C_j, I_j and R_j are already normalised as the proportion of the initial population, the sum of these proportions, $\sum_j [S_j(t) + C_j(t) + I_j(t) + R_j(t)]$, will remain 1 throughout the duration of each simulation.

A.6 Parameter values used in Chapter 3

Age Group	K	d	a
0-3 months	3.9415673	0.08654	0.15535
3-9 months	1.9418546	0.08654	0.15535
9-12 months	3.9415673	0.08654	0.15535
1-4 years	0.22615	0.01842	0.1434
5-9 years	0.183166	0.00377	0.0956
10-14 years	0.184199	0.00158	0.08365
15-19 years	0.183713	0.00261	0.0717
20-24 years	0.183208	0.00368	0.0478
25-29 years	0.182991	0.00414	0.03585
30-34 years	0.182921	0.00429	0.0239
35-39 years	0.182582	0.00501	0.0239
40-44 years	0.182187	0.00585	0.01195
45-49 years	0.18125	0.00785	0.01195
50-54 years	0.179814	0.01093	0.01195
55-59 years	0.176913	0.0172	0.01195
60-64 years	0.173196	0.02534	0.00239
65-69 years	0.165751	0.04202	0.00239
70-74 years	0.153113	0.07159	0.00239
75-79 years	0	0.2	0.00239

Table A.1 Parameter values for the age-dependent mortality rate, d_j, the age-dependent rate at which carriers develop disease, a_j and the rates of progression between age groups, K_j used in the model simulations in Chapter 3. The transfer rates K_j, were calculated from A.58. All units are $year^{-1}$.

Appendix B

SUPPLEMENT ARTICLE

Modeling Long-term Vaccination Strategies With MenAfriVac in the African Meningitis Belt

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Background. The introduction of MenAfriVac in campaigns targeting people aged 1–29 years across the African meningitis belt has successfully reduced meningitis incidence and carriage due to *Neisseria meningitidis* group A (MenA). It is important to consider how best to sustain population protection in the long term.

Methods. We created a mathematical model of MenA transmission and disease to investigate the potential impact of a range of immunization strategies. The model is age structured; includes classes of susceptible, carrier, ill, and immune people (who may be vaccinated or unvaccinated); and incorporates seasonal transmission and a stochastic forcing term that models between year variation in rates of transmission. Model parameters were primarily derived from African sources. The model can describe the typical annual incidence of meningitis in the prevaccine era, with irregular epidemics of varying size. Parameter and structural uncertainty were explored in sensitivity analyses.

Results. Following MenAfriVac introduction at high uptake, the model predicts excellent short-term disease control. With no subsequent immunization, strong resurgences in disease incidence were predicted after approximately 15 years (assuming 10 years' average vaccine protection). Routine immunization at 9 months of age resulted in lower average annual incidence than regular mass campaigns of 1- to 4-year-olds, provided coverage was above approximately 60%. The strategy with the lowest overall average annual incidence and longest time to resurgence was achieved using a combination strategy of introduction into the Expanded Programme on Immunization at 9 months, 5 years after the initial mass campaigns, with a catch-up targeting unvaccinated 1- to 4-year-olds.

Conclusions. These results can be used to inform policy recommendations for long-term vaccination strategies with MenAfriVac.

Keywords. meningitis; vaccine; Africa; mathematical modeling.

The African meningitis belt suffers from frequent large epidemics of meningococcal meningitis. A novel vaccine against *Neisseria meningitidis* group A (MenA), the major cause of epidemic meningitis, was developed through the Meningitis Vaccine Project (MVP), manufactured by the Serum Institute of India, Ltd [1]. The vaccine, known as MenAfriVac, was first introduced into Burkina Faso, Mali, and Niger in 2010 in mass immunization campaigns targeting 1- to 29-year-olds. MenAfriVac continues to be rolled out across the region, and >217 million individuals have been immunized to date. These campaigns have been remarkably successful in the short term in reducing the incidence of meningitis and the prevalence of MenA carriage, as shown in Burkina Faso [2, 3] and Chad [4]. To ensure that this success continues, long-term immunization strategies are required to maintain population protection.

Computational models have become an important tool for vaccine policy makers. By simulating the impact of a vaccine in silico, a wide range of vaccine strategies can be explored and the sensitivity of their predicted impact to structural and parameter uncertainty can be understood. Transmission dynamic models are essential to quantify both the direct and indirect (herd protection) effects of vaccination programs. For meningococcal infection, most transmission occurs between asymptomatic carriers, so any

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Clinical Infectious Diseases® 2015;61(S5):S594–600

DOI: 10.1093/cid/civ508

model attempting to capture the transmission dynamics of meningococci must essentially include the carrier state. This is especially relevant when considering the impact of MenAfriVac, given the evidence that MenA carriage is much reduced following MenAfriVac introduction [2, 4]. This is likely to give rise to large indirect vaccine effects, as seen with other conjugate vaccines [5]. Other key features of the epidemiology of MenA in the African meningitis belt must also be incorporated, which include the periodic but irregular nature of epidemics of varying size; the seasonality of meningitis with epidemics occurring in the dry season and dying out with the onset of the rains [6]; and the variation in disease risk [7] and carriage prevalence [8] by age.

A range of transmission models for meningococcal infection has been developed [9–11]. Only 2 have specifically examined MenA in the African meningitis belt. Irving et al [12] explored the potential mechanisms underlying the striking epidemiology in this region, showing that the complex and irregular timing of epidemics could be explained by the interaction of temporary immunity conferred by carriage of the bacteria together with seasonal changes in the transmissibility of infection. Tartof et al [13] used a transmission model to investigate different strategies using MenAfriVac.

Here we extend the transmission models of Irving et al [12] by addressing some of the limitations (such as the lack of age structure and wide parameter space considered), and incorporating vaccination. We utilize recently available MenA/MenAfriVac specific parameters and apply the model to investigate appropriate policy options for the sustained use of MenAfriVac.

METHODS

Model Structure

We developed a compartmental model that divides the population into the following states: (1) susceptible, (2) carrier of MenA, (3) disease due to MenA, and (4) recovered and immune, based on our previous investigations of simple deterministic models [12], and in vaccinated populations a mirror of these 4 states (Figure 1). The population is further structured by age into 19 age groups: 0 to <3 months, 3 to <9 months, 9 to <12 months, 1–4 years, 5–9 years, and 5-year age groups to age 80 years subsequently, with continuous aging between groups (rates of aging from one age group to another are given in Supplementary Table 1). The proportion of the population that is in each age group does not change over time.

Vaccination was implemented in different ways according to the strategy used (Table 1). For mass vaccination campaigns, we assumed that immunization occurred as a discrete event at one point in time, whereas routine immunization was implemented continuously as individuals reached the target age for the Expanded Programme on Immunization (EPI). The narrow age groups in <1-year-olds allowed routine vaccination to be implemented at different ages.

An important feature of the meningitis belt is the prominent seasonality [6] of disease, which we implemented through seasonal forcing of the transmission and invasion rates using a sinusoidal function [12]. The baseline transmission rate was varied stochastically drawing from a uniform distribution between 0.8 and 1.2 (ie, ±20%) each year to reflect between-year variation in transmission due to climatic [14] or other external

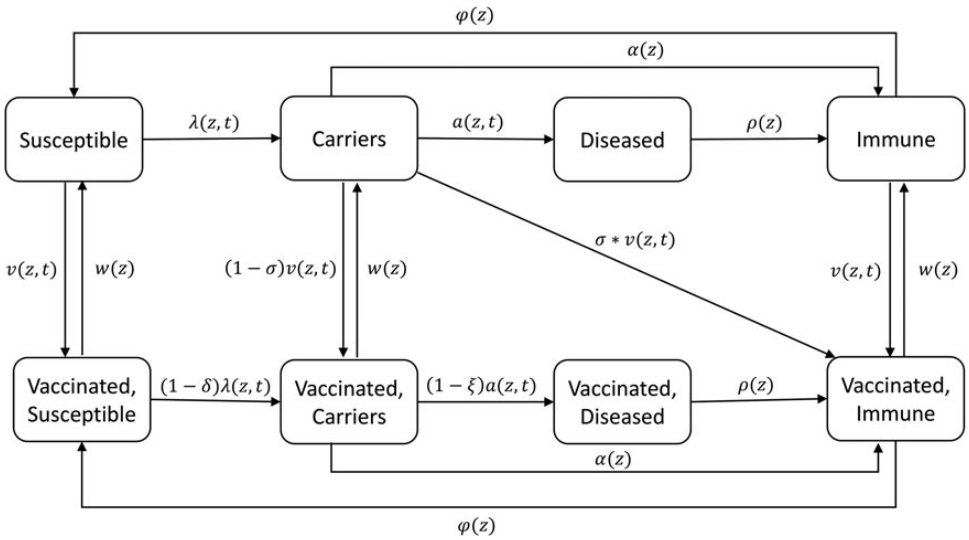

Figure 1. Diagram of the model for *Neisseria meningitidis* group A transmission and disease. Each compartment is divided into distinct age classes (not shown). See Table 1 for definition of parameters and Supplementary Material for the full model structure.

Table 1. Vaccination Strategies Considered

Vaccine Strategy	Introduction	Long-term
A. Initial campaign only	Mass immunization of 1- to 29-year-olds	Nothing
B. Periodic campaigns	Mass immunization of 1- to 29-year-olds	Periodic mass immunization of 1- to 4-year-olds
C. Routine EPI single dose	Mass immunization of 1- to 29-year-olds	Routine EPI at 9 mo, 5 y after introduction
D. Combination	Mass immunization of 1- to 29-year-olds	Routine EPI at 9 mo, 5 y after introduction, plus catch-up for 1- to 4-year-olds

Abbreviation: EPI, Expanded Programme on Immunization.

variability. To examine the sensitivity of results to this model structure, we introduced stochasticity in an alternative way, with weekly variation in transmission rates, drawn from the same uniform distribution (0.8–1.2). This "noisy" model used a method similar to the stochastic mechanism used by Tartof et al [13], but with the stochastic term drawn from a narrower range.

Full details of the model structure are given in the Supplementary Material, section A.

Model Parameters

Model parameters (Table 2) were based on the available literature, and African data wherever possible. Demographic parameters were based on Burkina Faso, a country at the heart of the meningitis belt. Different "who acquires infection from whom" (WAIFW) matrices were used and compared. In the absence of empirical data on population contact patterns, we used evidence on the age distribution of carriers during an MenA epidemic to inform these matrices [20]. The WAIFW matrix used is shown in Supplementary Figure 1; contacts are more intense between individuals in the same age group and particularly so for older children and young adults. It was necessary to estimate values for some parameters where direct evidence was lacking. In exploring the parameter space, it was apparent that there was a strong co-linear relationship between the transmission rate and duration of colonization. Direct estimation of model parameters is complicated by the intractability of the likelihood function for this model and the limitations of available incidence data. As a first exploration of model behavior to guide

Table 2. Model Parameters

Parameter	Parameter Name	Value	Unit	Comment [Reference]
Mortality rate	d	Age-specific	$Years^{-1}$	Census reports (Supplementary Table 2)
Recovery rate from disease	ρ	52	$Years^{-1}$	Disease lasts about a week [15]
Rate of loss of carriage	α	12	$Years^{-1}$	Only 1 study identified, suggesting 1-mo duration of MenA [16]
Transmission rate	β_0	10.5	. . .	Estimate
Rate at which carriers fall ill	a	Age-specific	$Years^{-1}$	Systematic review of case: carrier ratios [17], age-specific parameters estimated (Supplementary Table 3)
Rate of loss of immunity	ϕ	0.0839	$Years^{-1}$	Estimate, based on previous findings [12]
Seasonal forcing of transmission rate	ε_β	0.6	. . .	Estimate, based on previous findings [12]
Seasonal forcing of invasion rate	ε_a	0.6	. . .	Seasonality in invasion rate based on published systematic review [17]
Annual growth rate	q	0.0309	$Years^{-1}$	Census reports
Rate of progression between age groups	K	Age-specific	$Years^{-1}$	Estimated using mortality rates and annual population growth rate (Supplementary Table 2)
Vaccine efficacy against carriage	δ	0.6–0.9	Proportion	Range explored, 0.9 from [4]
Vaccine efficacy against disease	ξ	0.6–0.9	Proportion	Range explored, 0.9 from [4]
Carriage clearage upon vaccination	σ	0.9	Proportion	Unknown, effect explored in sensitivity analysis
Waning of vaccine protection	w	0.1	$Years^{-1}$	Consistent with findings from unpublished MVP trials. Varied in sensitivity analysis
Vaccination coverage for initial mass campaign	v_A	0.95	Proportion	Coverage surveys [18, 19]
Vaccination coverage for additional mass campaigns	v_B	0.6–0.8	Proportion	Unknown, range explored. 80% used in base case
Vaccination coverage for EPI	v_C	0.5–0.8	Proportion	Range taken from typical EPI coverage in meningitis belt countries. 80% used in base case

Abbreviations: EPI, Expanded Programme on Immunization; MenA, *Neisseria meningitidis* group A; MVP, Meningitis Vaccine Project.

inference, we found a number of different plausible combinations of parameter values for the transmission rate and duration of natural immunity, which were able to produce realistic results when used in our model and defined a possible range for the unknown parameters.

Model Implementation

The model was coded and run using the R package version 3.1.0, using the package deSolve to perform the numerical integration of differential equations. The time step was 1 day. For each simulation, we ran the model for a 20-year burn-in period before implementing the initial mass vaccination campaign in year 0. The model was then run for a further 40 years; all results are reported for this 40-year period. For each vaccination strategy, the average of 300 simulations was taken; this was based on a comparison of between 100 and 500 simulations that showed very small marginal differences between 300 and 500 simulations.

Vaccination Strategies

We considered a range of long-term vaccination strategies and compared these to a scenario without any vaccination and with only an initial mass vaccination campaign of 1- to 29-year-olds (Table 1). We also investigated the sensitivity of the results to changes in the age at EPI immunization and the coverage achieved for EPI immunization at 9 months.

RESULTS

Base Case

In the absence of preventive vaccination, the model was able to capture the distinctive epidemiology of meningococcal infection in the meningitis belt. A typical model run, with irregular epidemics of varying size, is shown in Figure 2.

Following initial mass vaccination of 1- to 29-year-olds, the model predicted a resurgence in disease after approximately 15 years, assuming an average of 10 years of vaccine protection (Figure 3).

Of the long-term immunization strategies considered, all were effective in maintaining control of disease. There was considerable overlap in the distribution of results (Figure 4), but routine EPI immunization at 9 months of age (strategy C) resulted in lower average annual incidence than regular mass campaigns of 1- to 4-year-olds (strategy B) under base case assumptions. Strategy C was superior to strategy B provided that EPI coverage was above approximately 60% (Table 3). The strategy with the lowest overall average annual incidence and longest time to resurgence was introduction into EPI at 9 months, 5 years after the initial mass campaigns, with a catch-up targeting unvaccinated children aged 1–4 years (strategy D).

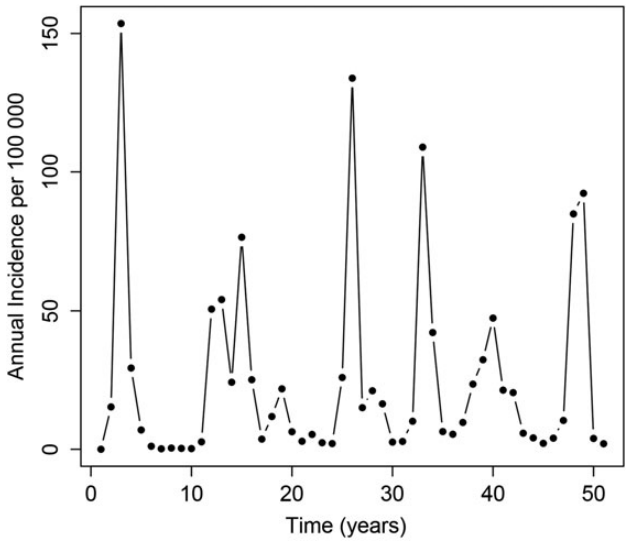

Figure 2. A typical run of the *Neisseria meningitidis* group A transmission model.

Sensitivity Analyses

We investigated the effect of changing some key model parameters and assumptions. In the absence of any long-term immunization (strategy A), assuming a shorter duration of protection resulted in disease incidence increasing more quickly; with 5 years of vaccine protection, the resurgence occurred after around 10 years (not shown).

For strategy C (routine EPI), as expected, as EPI coverage increased, the incidence of disease decreased (Table 3). For every 10% increase, the average annual incidence decreases by

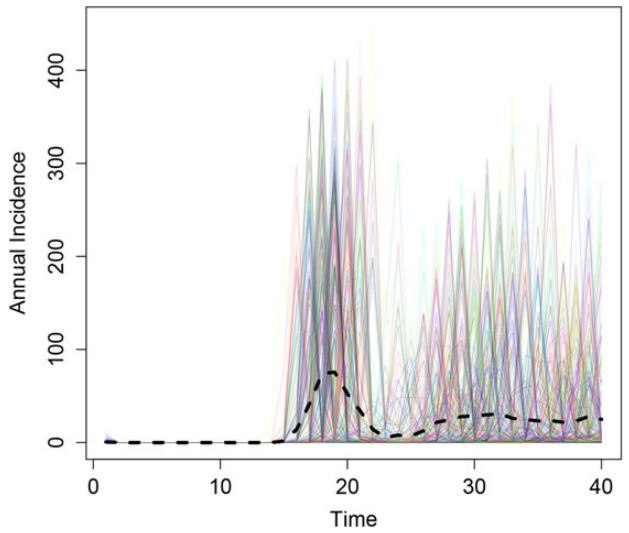

Figure 3. Results from 300 simulations of the initial mass immunization of 1- to 29-year-olds (implemented in year 0). The black dashed line depicts the mean annual incidence.

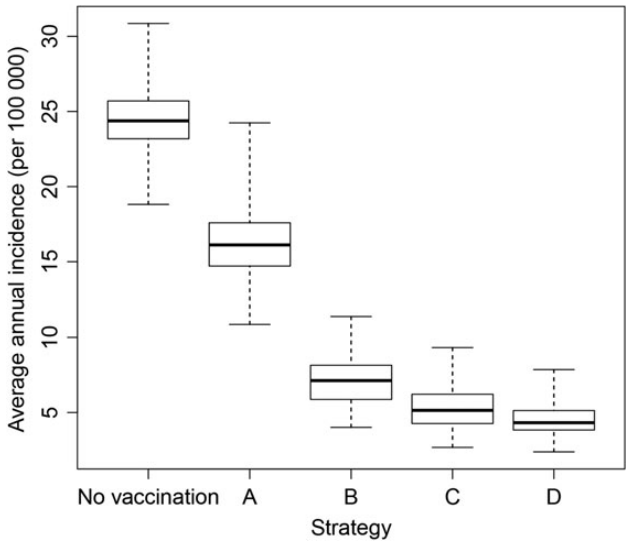

Figure 4. Box plot to show the median, interquartile range, and full range of the predicted annual incidence per 100 000 for different immunization strategies in the 40 years following vaccine introduction from 300 model simulations.

approximately 1 case per 100 000 population per year. Also consistent with expectations, disease control was better when vaccine effectiveness was higher (not shown).

We observed only marginal differences by varying the age at which routine MenAfriVac was given. The average disease incidence across all ages decreased as the age at immunization increased from 3 to 9 to 12 months of age. However, there were more cases in infants as the age at routine immunization increased. When averaged across 300 simulations, when MenAfriVac was given routinely at the age of 3 months, the model predicts an average annual incidence of 5.43 cases per 100 000 population per year in all ages and 4.67 cases per 100 000 individuals in infants, compared with the base case of immunization at 9 months (average incidence of 5.31 cases/100 000 across all ages and 8.77 cases/100 000 infants). Immunizing within EPI at 12 months of age results in an average annual incidence of 5.18 cases per 100 000 population, but 10.53 cases per 100 000 in infants.

The model results were insensitive to changes in the assumption of vaccine effectiveness against disease (ξ) when vaccine effectiveness against carriage (δ) was high (90%), because in this situation, carriage acquisitions were rare and so few people were at risk of disease downstream. Because it is unclear whether the vaccine can clear an episode of carriage, we also investigated the sensitivity of the results to changes in clearance upon vaccination. In the base case, we assumed that 90% of the carriers recover immediately after vaccination; when this proportion was changed to 10%, we found that the results were insensitive to the change.

The duration of natural immunity following carriage or disease is not known. In the base case, we assumed on average approximately 12 years' duration of immunity. When this was lowered to 7 years, keeping other parameters fixed, the incidence of disease under all scenarios was higher. However, the relative ranking of each strategy did not change.

The sensitivity of our results to changes in the model structure were also investigated. The results from the "noisy" model in which the transmission rate varied stochastically each week were very similar to the results presented above.

Table 3. Estimated Average Annual *Neisseria meningitidis* Group A Incidence per 100 000 in the 40 Years Following Vaccine Introduction Under Different Immunization Strategies and Coverage Assumptions

			Strategy B					
Age, y	No Vaccination	Strategy A Mass 1–29 y Only	Mass 1–29 y and EPI at 9 mo at 50% Coverage	Mass 1–29 y and EPI at 9 mo at 60% Coverage	Mass 1–29 y and EPI at 9 mo at 70% Coverage	Mass 1–29 y and EPI at 9 mo at 80% Coverage	Strategy C Mass 1–29 y and Periodic Mass Campaigns of 1–4 y	Strategy D Mass 1–29 y Plus EPI at 9 mo and 1–4 y Catch-up
<1	40.32	27.71	14.87	12.49	10.52	8.77	13.52	7.50
1–4	37.38	25.82	10.12	7.94	6.04	4.43	7.15	3.80
5–9	42.54	28.76	13.26	10.92	8.82	6.92	10.00	5.91
10–14	38.61	26.82	14.66	12.57	10.59	8.71	11.48	7.43
15–19	32.14	23.05	14.86	13.24	11.60	9.96	12.10	8.51
20–24	19.18	14.06	9.89	8.99	8.03	7.05	8.26	6.07
25–29	11.20	8.36	6.02	5.51	4.94	4.36	5.10	3.80
≥30	3.18	2.35	1.55	1.39	1.23	1.07	1.30	0.94
All	24.45	17.06	9.01	7.69	6.46	5.31	7.12	4.56

Unless otherwise stated, the coverage attained in the initial mass campaign among 1- to 29-year-olds was 95%, and routine and subsequent catch-up coverage was 80%.

Abbreviation: EPI, Expanded Programme on Immunization.

DISCUSSION

We developed a model of MenA transmission and disease that was able to describe the epidemiology observed in the African meningitis belt. We simulated the impact of the initial mass vaccination campaigns of 1- to 29-year-olds and predicted a period of very low incidence for at least 10 years, even when assuming a relatively short duration of protection. The indirect effects of the vaccine were clearly important in maintaining this low incidence postintroduction; we assumed a high degree of protection against carriage, consistent with the observed data [2, 4]. Following this honeymoon period, the model predicted a strong resurgence in disease incidence if there was no long-term immunization strategy. Of the long-term strategies we investigated, a combination strategy of routine EPI vaccination after 5 years together with a catch-up campaign targeting children aged 1–4 years who were born after the initial campaigns was the most effective, although there was considerable overlap in the distribution of results for different strategies. Routine EPI alone appeared to be more effective than periodic mass campaigns, unless EPI coverage was low (less than approximately 60%). The model findings, in addition to comprehensive information from clinical trials in children aged <1 year were presented to the World Health Organization's Strategic Advisory Group of Experts (SAGE) on immunization in October 2014 [21].

These findings suggest, first, that it is essential to implement a long-term strategy for the continued use of MenAfriVac. It is not sufficient for the vaccine only to be used in a large one-off campaign, as this may result in catastrophic resurgences in disease 10–20 years after vaccine introduction. All of the long-term strategies considered were effective in maintaining disease control, although for all strategies incidence was predicted to rise over the long term as population immunity from the initial campaigns waned. The inclusion of MenAfriVac into the routine EPI as a single dose at 9 months of age has the obvious advantage of using and likely strengthening existing infrastructure. The option to conduct periodic campaigns may, however, provide better disease control for those countries with very poor routine EPI uptake. The combination strategy of introduction into routine EPI with a one-off catch-up campaign targeting those born since the initial campaign was the most effective and also the most equitable option. Indeed, SAGE recommended that countries should adopt such a strategy within 5 years of campaign completion [22].

Our work has several strengths and limitations. Our model structure was based on extensive previous work that used a range of deterministic models, to explore the importance of seasonality and immunity following colonization [12]. As such, we feel we have good understanding of the underlying system dynamics. We extended these models to incorporate age structure and vaccination, and included a stochastic term so that the extent of seasonal forcing varied from year to year, to capture the effect of external forces (including, eg, dust or humidity conditions) [23]. We parameterized the model using appropriate published and unpublished data specific to African populations as far as possible. Some model parameters were unknown, including the transmission rate and duration of natural immunity. Here, we used a variety of methods to estimate a sensible range and feasible parameter combinations, ensuring that the model produced realistic results by comparing the model predictions to evidence on carriage prevalence by age, disease incidence by age, total annual incidence, seasonality, and periodicity. Further investigation of formal fitting methods such as Approximate Bayesian Computation is warranted [24], and more information on a range of parameters would be desirable, including age-specific contact patterns. Quantifying the duration of natural immunity following infection is particularly difficult; estimation is hampered by codependence with other parameters, and empirical measurement is problematic, not least because of the lack of an absolute correlate of protection [25]. We performed sensitivity analyses to investigate parameter uncertainty and showed that our findings were robust.

Our conclusions are different from another model of MenAfriVac, which found that mass campaigns were superior to routine EPI. This is probably largely because the duration of protection assumed by Tartof et al was much greater (essentially lifelong) for children immunized in campaigns than through EPI [13], whereas we assumed that protection in 1- to 4-year-olds would be similar to those immunized at the age of 9 months, based on recent data from the MVP's MenAfriVac trials. Tartof et al also used a different model structure, a larger time step, noncontinuous aging, a smaller number of simulations, and a higher frequency (weekly) and amplitude (0–0.75) of stochastic forcing. We chose a more parsimonious model structure that did not consider variable levels of protection against colonization and disease, as there was little evidence to inform such a structure and its parameterization. We explored the effect of other structural changes in our model, including the implementation of stochasticity as weekly variation in transmission rates, but this had minor effects on the model predictions and did not change our conclusions on the relative merits of each immunization strategy.

Following its introduction in 2010, MenAfriVac has been remarkably successful in controlling MenA disease. This success will not be maintained without a long-term immunization strategy. The early adopting countries will need to consider imminently how best to sustain population protection against MenA, and findings from mathematical models such as this can lend further support to decision makers at both the country level and internationally.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online (http://cid.oxfordjournals.org). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Notes

Acknowledgments. We thank the members of the World Health Organization (WHO) Immunization and Vaccines-Related Implementation Research Advisory Committee for critical review and helpful comments.

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Financial support. This work was funded by a grant from the Meningitis Vaccine Project (via PATH). C. L. T. received salary support from the MenAfriCar project, funded by grants from the Wellcome Trust and the Bill & Melinda Gates Foundation.

Supplement sponsorship. This article appears as part of the supplement "The Meningitis Vaccine Project: The Development, Licensure, Introduction, and Impact of a New Group A Meningococcal Conjugate Vaccine for Africa," sponsored by the Meningitis Vaccine Project through a grant from the Bill & Melinda Gates Foundation.

Potential conflicts of interest. A. J. K. C. has received institutional support from PATH and WHO. A. K. has received institutional support from PATH and WHO, and travel support from WHO to attend the SAGE meeting. C. L. T. has received institutional support from PATH and WHO, and Wellcome Trust and the Bill & Melinda Gates Foundation, and travel support from WHO to attend the SAGE meeting, and also has received consultancy fees from GlaxoSmithKline. M.-P. P. has received institutional support from PATH, Gavi the Vaccine Alliance, the Shefa Fund hosted by the Swiss Philanthropy Foundation, the National Philanthropic Trust, the Research Council of Norway, United States Agency for International Development, and the Research Council of Norway.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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SUPPLEMENT ARTICLE

Costs of *Neisseria meningitidis* Group A Disease and Economic Impact of Vaccination in Burkina Faso

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Background. Five years since the successful introduction of MenAfriVac in a mass vaccination campaign targeting 1- to 29-year-olds in Burkina Faso, consideration must be given to the optimal strategies for sustaining population protection. This study aims to estimate the economic impact of a range of vaccination strategies in Burkina Faso.

Methods. We performed a cost-of-illness study, comparing different vaccination scenarios in terms of costs to both households and health systems over a 26-year time horizon. These scenarios are (1) reactive vaccination campaign (baseline comparator); (2) preventive vaccination campaign; (3) routine immunization at 9 months; and (4) a combination of routine and an initial catchup campaign of children under 5. Costs were estimated from a literature review, which included unpublished programmatic documents and peer-reviewed publications. The future disease burden for each vaccination strategy was predicted using a dynamic transmission model of group A *Neisseria meningitidis*.

Results. From 2010 to 2014, the total costs associated with the preventive campaign targeting 1- to 29-year-olds with MenAfriVac were similar to the estimated costs of the reactive vaccination strategy (approximately 10 million US dollars [USD]). Between 2015 and 2035, routine immunization with or without a catch-up campaign of 1- to 4-year-olds is cost saving compared with the reactive strategy, both with and without discounting costs and cases. Most of the savings are accrued from lower costs of case management and household costs resulting from a lower burden of disease. After the initial investment in the preventive strategy, 1 USD invested in the routine strategy saves an additional 1.3 USD compared to the reactive strategy.

Conclusions. Prevention strategies using MenAfriVac will be significantly cost saving in Burkina Faso, both for the health system and for households, compared with the reactive strategy. This will protect households from catastrophic expenditures and increase the development capacity of the population.

Keywords. meningitis; case management; vaccination; economic impact; Burkina Faso.

Burkina Faso is one of the few countries whose boundaries lie wholly within the African "meningitis belt," and thus experiences a particularly high incidence of meningococcal meningitis, with epidemics occurring regularly [1, 2]. In 2010, Burkina Faso successfully implemented a nationwide preventive campaign with a new conjugate vaccine, known as MenAfriVac, against *Neisseria meningitidis* group A (MenA) [3, 4]. There have been no confirmed cases due to MenA in Burkina Faso since 2010 [2–5], and a substantial overall reduction in the meningitis burden [6], although group W remains a threat [7]. To sustain population-level protection against MenA following the 2010 introductory campaign, the country plans to incorporate MenAfriVac into the routine infant immunization schedule with 1 dose at the age of 9 months in late 2015 or early 2016 together with a single campaign among

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Clinical Infectious Diseases® 2015;61(S5):S473–82

DOI: 10.1093/cid/civ600

cohorts of children born since the campaign. This follows the recommendation made by the Strategic Advisory Group of Experts (SAGE) of the World Health Organization (WHO) in October 2014, which advised that meningitis belt countries should introduce MenAfriVac into the routine childhood immunization program within 5 years of campaign completion, together with a one-time catch-up campaign for young children born since the initial mass vaccination who would be outside the age window when the routine immunization program starts [8].

Prior to MenAfriVac introduction in 2010, the public health response to MenA relied on the detection of localized epidemics through surveillance and subsequent reactive immunization campaigns with polysaccharide vaccines [9] (as it still does for disease due to other meningococcal serogroups [10]). The effectiveness of this strategy is limited, largely because when vaccination campaigns are implemented, the epidemic may already be beyond its peak [11, 12]. Because this strategy does not prevent cases and epidemics from occurring, health systems can be severely disrupted and costs to the affected households can amount to one-third of the annual gross domestic product (GDP) per capita in Burkina Faso [13, 14].

This study aims to estimate the costs and savings of alternative preventive immunization strategies with MenAfriVac in Burkina Faso over a 26-year time period, compared with a reactive vaccination strategy.

METHODS

General Methodology

We estimate the economic impact of different MenA vaccination strategies in Burkina Faso, in terms of costs and savings for the health system and households and, as such, take a societal perspective. The study is a cost-of-illness study. By definition, cost-of-illness studies measure the economic burden of a disease and estimate the maximum amount that could be saved by reducing that burden [15].

We consider a 26-year time period, from 2010 until 2035, with 2010 being the year of the preventive campaign targeting 1- to 29-year-olds in Burkina Faso and 2015 the anticipated year of the introduction of routine MenAfriVac immunization. The study is both retrospective (real costs from 2010 to 2014) and prospective from 2015 onward, where future costs are projected. New cases are included during the entire study period. We therefore differentiate the time horizon into 2 periods: 2010–2014 and 2015–2035. The 2035 cutoff is based on an expected 10-year duration of protection of MenAfriVac against MenA and an expected waning of the effects of the 2010 campaign around 15 years after vaccine introduction, in the absence of further immunization [16].

The study compares the costs of reactive campaigns for individuals aged 2–30 years with a polysaccharide A + C meningococcal vaccine (reactive strategy) to each of the 3 new vaccination strategies aimed at preventing MenA using MenAfriVac while targeting different age groups : (1) a single preventive campaign in 2010 for individuals aged 1–29 years (preventive strategy); (2) routine immunization at 9 months of age 5 years after the preventive campaign (routine strategy); and (3) routine immunization at 9 months of age 5 years after the preventive campaign, and a catch-up of children born since the preventive campaign (combination strategy).

The incidence of MenA in each of the vaccination strategies is predicted from a transmission dynamic model of MenA and MenAfriVac immunization [16]. The model is designed to capture the typical epidemiology of MenA in the meningitis belt, with periodic but irregular epidemics occurring in the dry season. This model estimates the number of cases occurring per year on a national level and does not predict localized epidemics. Vaccination with MenAfriVac is implemented according to the

Table 1. Yearly Incidence Rate of Group A *Neisseria meningitidis* in Burkina Faso, 2011–2035

	Incidence Rate of MenA (per 100 000)		
Year	Preventive Campaign	Routine 1 Dose	Routine + Catch-up
1	0	0	0
2	0	0	0
3	0	0	0
4	0	0	0
5	0	0	0
6	0	0	0
7	0	0	0
8	0	0	0
9	0	0	0
10	0	0	0
11	0	0	0
12	0.0001	0	0
13	0.0022	0	0
14	0.075	0	0
15	1.4	0	0
16	14.1	0.00017	0
17	40.98	0.013	0
18	73.9	0.14	0
19	75.6	0.32	0
20	52.4	0.93	0.0003
21	34.17	3.41	0.038
22	14.19	4.26	0.35
23	5.49	9.59	0.93
24	7.89	16.6	3.17
25	6.85	15.7	5.9

The considered incidence of MenA in the absence of any preventive strategy is 24.7 per 100 000.

Abbreviation: MenA, *Neisseria meningitidis* group A.

strategies above, and influences disease epidemiology through effectiveness against disease and carriage (90% in both cases), thus providing direct and indirect protection. In the model, MenAfriVac coverage is assumed to be 95% for the 2010 campaign and 80% for routine and subsequent catch-up. The number of cases of MenA is estimated by applying the annual incidence rates shown in Table 1 to the population of Burkina Faso [17].

Costs and cases are primarily undiscounted, but we also explored the sensitivity of results to 2 alternative discounting scenarios: discounting of 3% for both cases and costs and discounting of costs at 3% with no discounting of cases. All costs were adjusted to 2012 US dollars (USD). For the period 2015–2035, the price of vaccines is an average of the expected price during that period.

Cost Calculation

Different types of costs are calculated: (1) the costs of case management and of vaccination for the health system, and (2) the direct nonmedical costs (DNMCs) and indirect costs (ICs) for households. We assume that case management of meningitis is free for households and is all supported by the health system, according to the policy promoted by the international community during epidemics of meningitis in Burkina Faso [9]. We further assume that in households there is no self-medication nor visit to a traditional healer prior to contact with a health center or hospital. Both these assumptions are conservative. Costs of sequelae have not been taken into account.

Health System Costs

The case management costs are calculated by multiplying the estimated number of cases of MenA under each strategy by an average cost of case management calculated using a multilinear regression analysis including data from 27 countries on the direct medical costs (DMCs) of meningitis cases in low- and middle-income countries [18]. Original data for Burkina Faso come from Colombini et al [13].

The costs of reactive campaigns are based on the total costs of reactive vaccination estimated in a study performed in Burkina Faso in 2007 [14], divided by the number of cases in that study period to give an average cost per case. The average cost per case is then multiplied by the estimated incidence of cases of MenA under a reactive strategy between 2010 and 2035. In reality, reactive vaccination only occurs when an epidemic threshold is reached, so only cases that occur in areas that reach an epidemic threshold will yield a reactive vaccination cost. As the model does not predict the occurrence of localized outbreaks, it is not possible to mirror the true policy.

As an alternative, we estimated the cost of reactive vaccination based on the number of affected districts in Burkina Faso that were immunized in the last MenA epidemic in 2006–2007. Here we assumed that a similar epidemic would occur every 10 years, requiring reactive campaigns in 46 districts with 1 district per year requiring a reactive campaign in interepidemic years. The median district population size in Burkina Faso in 2010 was 233 315, and we assumed that 75% of the district population would be targeted (as a proxy for those aged 2–30 years) at a cost of 1.45 USD per person vaccinated [14].

The cost of the preventive campaign was derived from the WHO report on the 2010 preventive campaign in Burkina Faso and Gavi financial documents and includes total vaccine costs and total delivery costs. The costs of vaccination of the other strategies is based on (1) the unit delivery costs derived from a review of national program documents; (2) the projection of fully loaded price for vaccines and injection supplies per dose; and (3) an estimate of the number of doses required for each strategy given the target population estimated from United Nations population data [17]. The average delivery cost per dose of the catch-up campaign is considered to be the same as for the preventive campaign. The average delivery cost per dose of routine vaccination is derived from the data available on the comprehensive multiyear plan of the immunization program in Burkina Faso [19], which consists of the sum of the specific costs of all the activities needed to administer routine vaccines, divided by the total number of vaccine doses supplied (see Table 2 for more details). We assume that there are no fixed costs and that the cost of immunization is shared proportionally to the number of doses.

The number of doses of vaccines required is based on the target population, the expected coverage rate, and wastage rates of each vaccination strategy (Table 3).

Household Costs

Two types of costs for households are taken into account: DNMCs and ICs.

DNMCs are nonmedical costs incurred by the patient and/or the family carer because of the illness episode. For instance, in Burkina Faso, hospitals do not provide certain services (meals, hygiene) and there is hardly any transport or ambulance service. Consequently, households have to bear these transport costs, even for seriously ill patients. The family carers also have to pay for food for the patient and themselves, and buy soap and other personal hygiene items. Additionally, DNMCs include phone calls to family and costs for visitors (Table 2). This DNMC is calculated by multiplying Portnoy et al's DMC [18] by the ratio of DNMC and DMC in Burkina Faso from Colombini et al's original data ($r = 0.61$) [13].

ICs are estimated as the loss of income due to a temporary work interruption, calculated by multiplying the average number of days of illness (from [13]) by the daily per capita GDP (from the World Bank [20]). We considered that only 1 adult

Table 2. Elements of the Methodology: Mean Costs Used in the Study and Other Methodological Points on Cost Calculation

	Cost Parameters[a]	Sources of Data	Methodological Notes
All Strategies	Mean Cost per Case		
Case management costs for the health system	50.73	Portnoy et al [18] Colombini et al [13]	Field study in Burkina Faso during the epidemic season (2006–2007) Cost includes prepositioning and distribution of medicines during epidemics, district laboratory analyses for case diagnosis and choice of treatment, patient care Multiple regression analysis (Portnoy et al [18])
DMCs for households	. . .		Hypothesis (conservative): Medical care of meningitis is free of charge for households; all case management costs are captured at the health system level Households do not seek informal care
DNMCs for households	31.08	Portnoy et al [18] Colombini et al [13]	Field study in Burkina Faso during the epidemic season (2006–2007) Costs includes transport, foods, costs for visitors, phone calls to the family, personal hygiene items Prorata of DMCs of Portnoy et al [18] as per the share between DNMCs and DMCs in Colombini et al [13]
Indirect costs for households	129.55	World Bank (GDP per capita); Colombini [13] (duration of inactivity)	Hypothesis (conservative): Duration of professional inactivity due to the illness = 21 days No. of persons impeded to work in the households = 1 Sequelae impact is not included here Formula of calculation: No. of days of inactivity × GDP/capita/day
Reactive vaccination campaign			
Vaccination			
Campaigns	263.25	Colombini et al [14]	Field study in Burkina Faso during the epidemic season (2006–2007). Includes meningococcal polysaccharide A/C vaccines and injection supplies; per diems and allowances for human resources; planning, training, social mobilization, monitoring, supervision and assessment of the immunization campaigns; management of cases of AEFIs; waste management; planning of overall surveillance and response activities (preepidemics)
Surveillance and other support activities	14.89	Colombini et al [14]	Field study in Burkina Faso during the epidemic season (2006–2007) Includes training, social communication on meningitis, investigation of suspected cases, laboratory case confirmation and etiologic identification, supervision, coordination of actors for surveillance and response activities
Preventive vaccination campaign			
Vaccination			
Delivery	Total costs	Gavi commitments and disbursements; countries application; campaigns evaluation report	Includes per diems and allowances for human resources; planning, training, social mobilization, monitoring, supervision and assessment of the immunization campaigns; surveillance; waste management; coordination, and partnership
Vaccine and injection material	Total costs	Gavi	Includes doses of MenAfriVac and injection supplies
Routine 1 dose, at 9 mo of age			
Vaccination	Mean Cost per Dose		
Delivery	0.28	cMYP Burkina Faso 2011–2015	Includes service delivery, advocacy and communication, monitoring and disease surveillance, program management. For comparison purpose, it does not include shared and capital costs (buildings, salaries of personnel, vehicles, and cold chain equipment)
Vaccine and injection material	0.90	MVP	Fully loaded price—includes doses of MenAfriVac, injection supplies and freight. Average price on the projection period (2015–2035)
Catch-up campaign			
Vaccination	Mean Cost per Dose		
Delivery	0.24	Current study	Hypothesis: The average delivery cost per dose for catch-up campaigns is the same as in the 2010 preventive campaigns
Vaccine and injection material	0.73	MVP	Fully loaded price—includes doses of MenAfriVac, injection supplies, and freight. Price as of 2015

Abbreviations: AEFI, adverse events following immunization; cMYP, comprehensive multiyear plan; DMC, direct medical cost; DNMC, direct nonmedical cost; GDP, gross domestic product; MVP, Meningitis Vaccine Project.

[a] Value in 2012 US dollars.

Table 3. Target Population, Coverage Rate, Wastage Factor, and Buffer Stock for Routine Vaccination and Preventive and Catch-up Campaigns Against Group A *Neisseria meningitidis*

Parameters	Routine Vaccination (2015–2035)	Catch-up Campaign (2015)	Preventive Campaigns (2010)
Total target population[a]	15 795 911	2 431 328	11 023 447
Coverage rate	80%	100%	100%[b]
Total effective target population[c]	12 212 780	2 995 304	11 023 447
Wastage factor	1.67	1.15	1.15
Buffer stock	25%	0%	0%
Total No. of vaccine doses[d]	20 643 066	2 796 027	12 205 400[e]

[a] For the preventive campaigns, the target population is the one of 2010 only as the campaign is implemented only once during the total period.

[b] Rate based on administrative coverage, used for the calculation of costs. A lower rate of 95%, based on a coverage survey estimate, is used for assessment of the epidemiological impact.

[c] Routine effective target population = surviving infant population × rollout factor (accounting for partial year introduction in the first year) × coverage. Campaign effective target population = target population (assuming a plan to cover 100% of the target population).

[d] Number of doses = [effective target population × wastage factor] + buffer. Buffer applies to routine only; for year x = 0.25 × [doses year x – Doses year x – 1] if this difference is positive; otherwise buffer = 0.

[e] Source: World Health Organization. Summary report on the 2 phase meningitis vaccination campaign in Burkina Faso, January 2011.

person per case was affected by work interruption: either the patient, if the patient is an adult, or 1 adult caregiver if the patient is a child.

Savings and Economic Impact

The economic impact is estimated from the costs saved by both households and the health system. Savings are calculated as the difference between the costs of the baseline strategy (reactive strategy) and each alternative strategy over the same period of time; if the differential is positive, the alternative strategy is cost saving. The savings are subdivided by cost category (case management, vaccination, DNMCs, ICs).

RESULTS

Impact on Disease Burden

The number of cases of MenA expected in Burkina Faso varies from one strategy to the other (more detail is given in [12]). In the absence of preventive vaccination, 122 466 cases are predicted between 2015 and 2035. In contrast, the most effective combination strategy predicts only 3066 cases over the same period (Table 4). The 3 alternative strategies considerably reduce the number of cases of MenA, preventing at least 100 000 cases compared with the reactive strategy.

Impact on Costs

The reactive strategy led to higher total costs both for the health system and for households, regardless of the comparison strategy (Table 4).

Total Undiscounted Costs

From 2010 to 2014, the costs of the preventive and the reactive strategy are almost the same, with 9.7 and 10.0 million USD, respectively (3.1% difference). However, the structure of the costs are very different: the cost of the preventive campaigns is 1.7 times that of the reactive campaigns, but there are no costs associated with cases under the preventive strategy as no MenA cases occurred during this time period.

Between 2015 and 2035, the cost of the reactive strategy is calculated as 59.9 million USD. By comparison, from 2015 to 2035 the routine and the combination strategies would cost a total of 27.4 to 24.6 million USD, respectively. De facto, the total cost for the reactive strategy is 2.2 times higher than the routine and the combination strategies. This is explained both by a higher number of cases of MenA, resulting in higher costs of case management and of DNMC and IC for households, and the higher costs of vaccination. The costs of the routine and the combination strategies are very similar due both to the low costs of the catch-up campaign in 2015 and to the lowest incidence of MenA under the combination strategy yielding lower case management costs, DNMCs, and ICs.

Within each strategy, total vaccination costs are higher than those linked to care of cases (case management, DNMCs, and ICs), due to vaccination leading to a decreased number of cases—and thus to a reduction of the costs linked to illness.

Costs for the Health System

A huge decrease in the costs of case management is observed for all preventive strategies compared with the reactive strategy, as many fewer cases are predicted to occur (Table 4). With routine and combination strategies, the costs of case management are only 2.7% and 0.6%, respectively, compared with 10.4% for the reactive strategy between 2015 and 2035.

Between 2010 and 2014, the health system costs associated with vaccination were higher for the preventive strategy, as all

Table 4. Costs of Different Strategies of Vaccination Against Group A *Neisseria meningitidis*, Burkina Faso, 2010–2035

		Health System			Households			
Strategy	No. of Cases of MenA	Costs Case Management	Costs Vaccination	Subtotal	Direct Nonmedical Costs	Indirect Costs	Subtotal	Total
Reactive strategy								
2010–2014	20 453	1 037 575	5 688 847	6 726 422	635 669	2 649 616	3 285 284	10 011 706
2015–2035	122 466	6 212 720	34 063 283	40 276 002	3 806 212	15 865 184	19 671 396	59 947 398
1. Preventive strategy								
2010–2014	0	0	9 713 805	9 713 805	0	0	0	9 713 805
2. Routine strategy								
2015–2035	14 776	749 577	24 282 338	25 031 915	459 227	1 914 166	2 373 393	27 405 308
3. Combination strategy								
2015–2035	3066	155 550	27 000 288	27 155 838	95 298	397 223	492 520	27 648 358

Data are presented as US dollars unless otherwise specified.

Abbreviation: MenA, *Neisseria meningitidis* group A.

1- to 29-year-olds in Burkina Faso were targeted nationwide, with costs concentrated in one single month in a single year (December 2010). By contrast, reactive campaigns selectively target districts experiencing epidemics and not the national population.

Between 2015 and 2035, vaccination costs of the reactive strategy are 1.4 to 1.3 times higher than those of the routine and the combination strategies, respectively (Table 4). The average vaccination cost per vaccinee is higher for routine vaccination than for preventive campaigns, with 1.99 USD and 0.88 USD respectively.

Costs for Households

The total cost for households is directly linked to the burden of disease: the fewer the cases, the lower the costs. All of the alternative strategies are less costly than the reactive strategy (Table 4), with the combination strategy resulting in the lowest household costs. ICs, which represent here the loss of earnings for the family during the acute illness episode and the recovery, represent the main costs to households (81%).

Net Savings for Both the Health System and the Households

All the alternative strategies save money compared with the reactive strategy (Table 5, Figure 1). In total, the savings for the routine and the combination strategy are similar and amount to 32.5 and 32.3 million USD between 2015 and 2035, respectively. Savings are higher overall for the households than for the health system.

Between 2010 and 2014, the savings are much lower (about 300 000 USD); there are no cases of MenA thanks to the preventive campaign, but this mass campaign was costly in terms of vaccination costs.

Ultimately, each dollar invested in routine immunization generates savings of an additional 1.3 USD, and each dollar invested in the combination strategy saves 1.2 USD.

Sensitivity Analysis: Impact of Discounting

If discounting the costs at 3%, all the alternative strategies are still cost-saving both for the health system and for the households. However, the savings are lower than in the undiscounted

Table 5. Cost Savings of Various Strategies of Vaccination Against Group A Meningococcus, Burkina Faso, 2010–2035

		Health System (USD)			Households Savings (USD)			
Strategy	No. of Cases Averted	Case Management	Vaccination	Subtotal	Direct Nonmedical Costs	Indirect Costs	Subtotal	Total Savings (USD)
1. Preventive strategy, 2010–2014	20 453	1 037 575	−4 024 958	−2 987 383	635 669	2 649 616	3 285 284	297 901
2. Routine strategy, 2015–2035	107 690	5 463 143	9 780 945	15 244 088	3 346 985	13 951 018	17 298 003	32 542 090
3. Combination strategy, 2015–2035	119 400	6 057 170	7 062 995	13 120 165	3 710 914	15 467 961	19 178 875	32 299 040

Abbreviation: USD, US dollars.

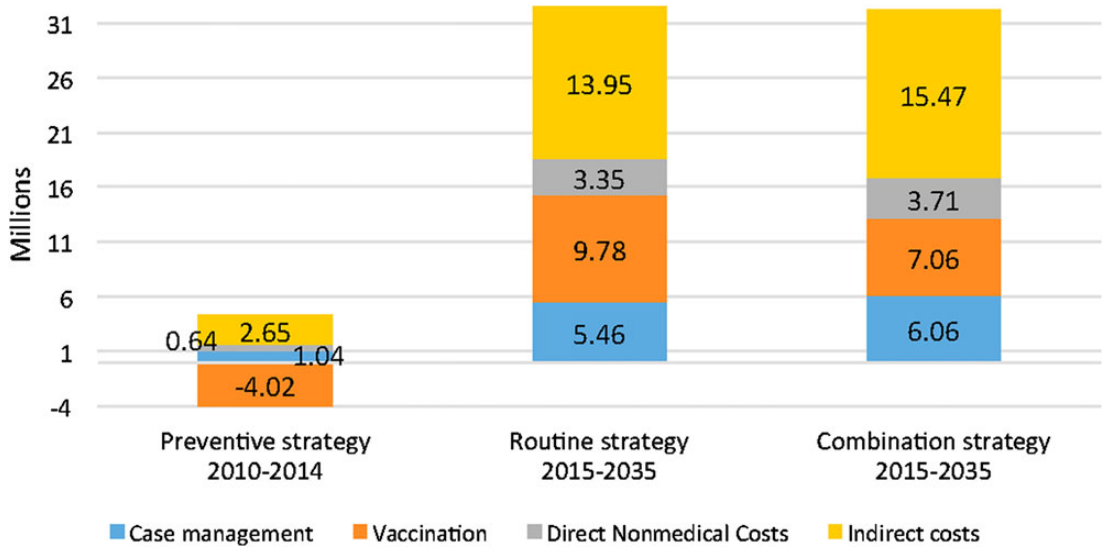

Figure 1. Savings (in millions of US dollars) of the 3 strategies, Burkina Faso, 2010–2035.

scenario and amount to 17.8–18 million USD for the combination and the routine strategies, respectively (Figure 2). The only exception is again for vaccination, strictly speaking, under the preventive strategy between 2010 and 2014.

When discounting both cases and costs at 3%, the preventive strategy costs 1.2 million USD more than the reactive strategy between 2010 and 2014. The long-term strategies remain cost-saving, with savings amounting to a maximum of 3.9 million USD for the routine strategy between 2015 and 2035. However, in this scenario vaccination costs are higher for each of the alternative strategies than for the reactive strategies (Figure 3).

DISCUSSION

We find that the introduction and sustained use of MenAfriVac to prevent MenA has a substantial positive economic impact in Burkina Faso. Each of the preventive strategies considered

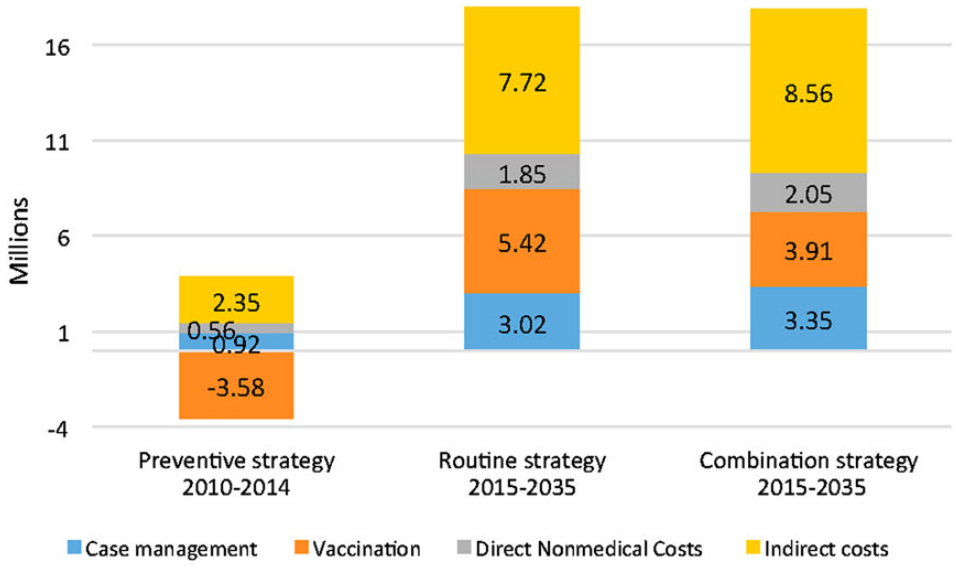

Figure 2. Discounted savings (in millions of US dollars) of the 3 strategies, Burkina Faso, 2010–2035. Savings are calculated based on a discounting of costs at a rate of 3%, but no discounting of cases (discount rate = 0%).

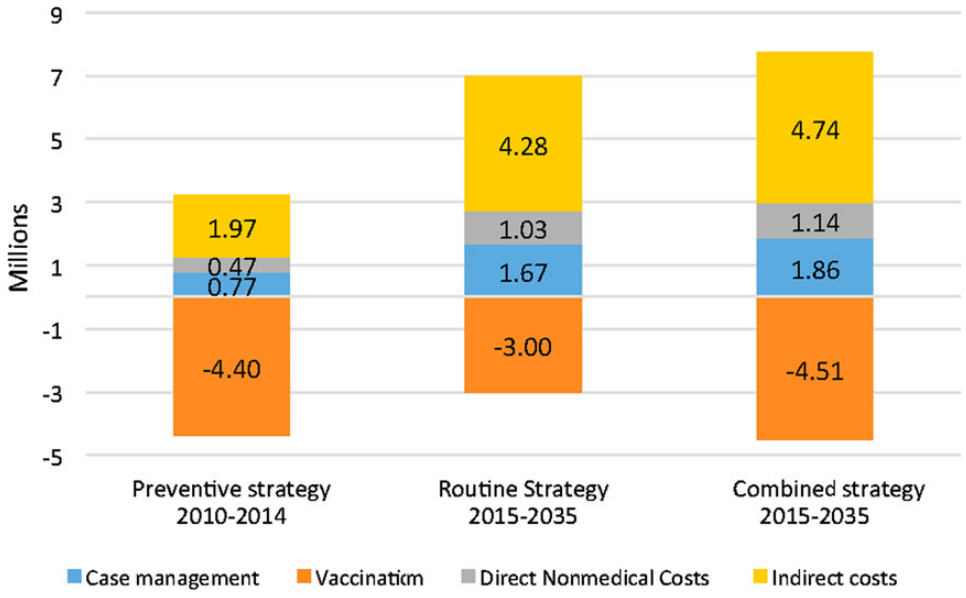

Figure 3. Discounted savings (in millions of US dollars) of the 3 strategies, Burkina Faso, 2010–2035. Savings relied on discounted costs and discounted cases at a discount rate of 3%.

generates considerable savings compared to the reactive strategy using a polysaccharide vaccine between 2015 and 2035, both with and without discounting costs at 3%. Indeed, each dollar invested in the combination strategy recommended by SAGE saves an additional 1.2 USD; in total, up to 32.3 million USD can be saved. Savings to the health system are accrued by lower costs of case management, and in the long term, also through reduced vaccination costs. By preventing MenA, MenAfriVac will reduce the economic burden on households and save thousands of households from catastrophic expenditures and pauperization [11]. Meningitis prevention is also likely to raise population well-being and development capacity including through the improvement of child health [21–24]. The severe disruption to the health system and communities from meningitis epidemics will be avoided [14, 25].

Our methodological choices were conservative and, thus, we may have underestimated the economic benefits of MenAfriVac. The costs to households may be underestimated for several reasons. We assumed that costs of case management are entirely supported by the health system; however, although care is supposed to be free of charge during an epidemic, an earlier study in Burkina Faso [13] estimated that 96% of households paid for all or part of the care. In addition, 34% of households report self-medication before going to a health center or a hospital, and 23% seek traditional care. The ICs were based on the assumption that only 1 person was prevented from working. In reality, this can only be true when the patient is a child, and although most cases occur in children, adults are still affected by MenA [26]. Household costs do not include either the direct or ICs associated with sequelae, which affect 9.5% of survivors [27], and may be severe and costly [13, 28]. Moreover, recent experimental economic studies propose widening the scope of ICs by also including monetary estimates of interruptions in education schooling and the impact on cognitive development [21–23]. Last, the focus here is on the economic impact on households and costs and savings for the health system. A later study will also include the macroeconomic impact and the financial risk protection of households [29].

Our estimates of the epidemiological impact of MenAfriVac from 2015 through 2035 are based on a transmission dynamic model of MenA [16]. Different MenAfriVac coverage estimates are used for the transmission model and the economic costs. For the 2010 campaign, costs are based on administrative coverage, whereas epidemiological impact uses a lower coverage survey estimate [3]; the overall effect is conservative. The transmission model predicts a national incidence and does not predict the occurrence of local epidemics that would trigger a reactive vaccination response. We have estimated the costs of reactive vaccination on a per-case basis. However, the costs of reactive vaccination could be lower if the geographical distribution of MenA cases was such that not all occur in districts that reach the epidemic response threshold. To address this, we used an alternative method of estimating costs of reactive vaccination, based on the number of district-level epidemic response campaigns conducted in Burkina Faso in the pre-MenAfriVac era and assuming a major epidemic every 10 years, and estimated

costs to be around 10% higher. A further consideration is that we have not estimated the cases prevented through a reactive strategy. The effectiveness of reactive vaccination has not been systematically reviewed and critically depends on the speed at which reactive vaccination can be implemented [12]. However, it is not thought to be a highly effective strategy, hence the development and introduction of MenAfriVac. In addition, we are using an estimate of disease incidence that is typical for a meningitis belt country, although not necessarily a high-incidence country such as Burkina Faso. On balance, we therefore conclude that our estimates of the costs of reactive vaccination are conservative.

The introduction of MenAfriVac across the African meningitis belt has dramatically reduced the burden of MenA disease. With appropriate long-term immunization strategies as recommended by SAGE, this remarkable success promises to continue. The economic impact of MenAfriVac is illustrated here for Burkina Faso, and adds to the evidence on the remarkable public health success of this vaccine.

Notes

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Acknowledgments. We thank the Meningitis Vaccine Project (MVP) and the WHO for supporting the research. Special thanks go to Monique Berlier (MVP), Olivia Cohen (intern at WHO), and Mamoudou Djingarey, Katya Fernandez, and Jacqueline Lee Endt from WHO for their help in providing helpful data to conduct the study; and also to Raymond Hutubessy (WHO) for his advice on some methodological points.

Supplement sponsorship. This article appears as part of the supplement "The Meningitis Vaccine Project: The Development, Licensure, Introduction, and Impact of a New Group A Meningococcal Conjugate Vaccine for Africa," sponsored by the Meningitis Vaccine Project through a grant from the Bill & Melinda Gates Foundation.

Potential conflicts of interest. M.-P. P. has received institutional grant support from PATH, Gavi the Vaccine Alliance, the Shefa Fund hosted by the Swiss Philanthropy Foundation, the National Philanthropic Trust, the Research Council of Norway, and the US Agency for International Development, and has received travel support from PATH and the Research Council of Norway. All other authors report no potential conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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Appendix C

Set of differential equations describing EPI at 5 years

Fist age group

$$\frac{dS_1}{dt} = B_t N + \phi R_1 - \theta\lambda_1 S_1 - (age + \mu_{1,t})S_1 + w_L SV_1 + w_S SE_1$$
$$\frac{dC_1}{dt} = \theta\lambda_1 S_1 + (a_1 - \alpha - \mu_{1,t} - age)C_1 + w_L CV_1 + w_S CE_1$$
$$\frac{dI_1}{dt} = a_1 C_1 - (\rho + age + \mu_{1,t})I_1$$
$$\frac{dR_1}{dt} = \rho I_1 + \alpha C_1 - (\phi + age + \mu_{1,t})R_1 + w_L RV_1 + w_S RE_1$$
$$\frac{dSV_1}{dt} = -(1-\delta)\theta\lambda_1 SV_1 + \phi RV_1 - (w_L + age + \mu_{1,t})SV_1$$
$$\frac{dCV_1}{dt} = (1-\delta)\theta\lambda_1 SV_1 - ((1-\xi)a_1 + \alpha + w_L + age + \mu_{1,t})CV_1$$
$$\frac{dIV_1}{dt} = (1-\xi)a_1 CV_1 - (\rho + age + \mu_{1,t})IV_1$$
$$\frac{dRV_1}{dt} = \rho IV_1 + \alpha CV_1 - (\phi + w_L + age + \mu_{1,t})RV_1$$
$$\frac{dSE_1}{dt} = -(1-\delta)\theta\lambda_1 SE_1 + \phi RE_1 - (w_S + age + \mu_{1,t})SE_1$$
$$\frac{dCE_1}{dt} = (1-\delta)\theta\lambda_1 SE_1 - ((1-\xi)a_1 + \alpha + w_S + age + \mu_{1,t})CE_1$$
$$\frac{dIE_1}{dt} = (1-\xi)a_1 CE_1 - (\rho + age + \mu_{1,t})IE_1$$
$$\frac{dRE_1}{dt} = \rho IE_1 + \alpha CE_1 - (\phi + w_S + age + \mu_{1,t})RE_1$$

Age groups $i = 2, ..., 5$ & age groups $i = 7, ..., 99$

$$\frac{dS_i}{dt} = ageS_{i-1} + \phi R_i - \theta\lambda_i S_i - (age + \mu_{i,t})S_i + w_L SV_i + w_S SE_i$$
$$\frac{dC_i}{dt} = ageC_{i-1} + \theta\lambda_i S_i + (a_i - \alpha - \mu_{i,t} - age)C_i + w_L CV_i + w_S CE_i$$
$$\frac{dI_i}{dt} = ageI_{i-1} + a_i C_i - (\rho + age + \mu_{i,t})I_i$$
$$\frac{dR_i}{dt} = ageR_{i-1} + \rho I_i + \alpha C_i - (\phi + age + \mu_{i,t})R_i + w_L RV_i + w_S RE_i$$
$$\frac{dSV_i}{dt} = ageSV_{i-1} - (1-\delta)\theta\lambda_i SV_i + \phi RV_i - (w_L + age + \mu_{i,t})SV_i$$
$$\frac{dCV_i}{dt} = ageCV_{i-1} + (1-\delta)\theta\lambda_i SV_i - ((1-\xi)a_i + \alpha + w_L + age + \mu_{i,t})CV_i$$
$$\frac{dIV_i}{dt} = ageIV_{i-1} + (1-\xi)a_i CV_i - (\rho + age + \mu_{i,t})IV_i$$
$$\frac{dRV_i}{dt} = ageRV_{i-1} + \rho IV_i + \alpha CV_i - (\phi + w_L + age + \mu_{i,t})RV_i$$
$$\frac{dSE_i}{dt} = ageSE_{i-1} - (1-\delta)\theta\lambda_i SE_i + \phi RE_i - (w_S + age + \mu_{i,t})SE_i$$
$$\frac{dCE_i}{dt} = ageCE_{i-1} + (1-\delta)\theta\lambda_i SE_i - ((1-\xi)a_i + \alpha + w_S + age + \mu_{i,t})CE_i$$
$$\frac{dIE_i}{dt} = ageIE_{i-1} + (1-\xi)a_i CE_i - (\rho + age + \mu_{i,t})IE_i$$
$$\frac{dRE_i}{dt} = ageRE_{i-1} + \rho IE_i + \alpha CE_i - (\phi + w_S + age + \mu_{i,t})RE_i$$

Age group 6

$$\frac{dS_6}{dt} = (1-\gamma_t)ageS_5 + \phi R_6 - \theta\lambda_6 S_6 - (age + \mu_{6,t})S_6 + w_L SV_6 + w_S SE_6$$
$$\frac{dC_6}{dt} = (1-\gamma_t)ageC_5 + \theta\lambda_6 S_6 + (a_6 - \alpha - \mu_{6,t} - age)C_6 + w_L CV_6 + w_S CE_6$$
$$\frac{dI_6}{dt} = ageI_5 + a_6 C_6 - (\rho + age + \mu_{6,t})I_6$$
$$\frac{dR_6}{dt} = (1-\gamma_t)ageR_5 + \rho I_6 + \alpha C_6 - (\phi + age + \mu_{6,t})R_6 + w_L RV_6 + w_S RE_6$$
$$\frac{dSV_6}{dt} = ageSV_5 - (1-\delta)\theta\lambda_6 SV_6 + \phi RV_6 - (w_L + age + \mu_{6,t})SV_6 + \gamma_t ageS_5$$
$$\frac{dCV_6}{dt} = ageCV_5 + (1-\delta)\theta\lambda_6 SV_6 - ((1-\xi)a_6 + \alpha + w_L + age + \mu_{6,t})CV_6 + \gamma_t C_5$$
$$\frac{dIV_6}{dt} = ageIV_5 + (1-\xi)a_6 CV_6 - (\rho + age + \mu_{6,t})IV_6$$
$$\frac{dRV_6}{dt} = ageRV_5 + \rho IV_6 + \alpha CV_6 - (\phi + w_L + age + \mu_{6,t})RV_6 + \gamma_t R_5$$

$$\frac{dSE_6}{dt} = ageSE_5 - (1-\delta)\theta\lambda_6 SE_6 + \phi RE_6 - (w_S + age + \mu_{6,t})SE_6$$
$$\frac{dCE_6}{dt} = ageCE_5 + (1-\delta)\theta\lambda_6 SE_6 - ((1-\xi)a_6 + \alpha + w_S + age + \mu_{6,t})CE_6$$
$$\frac{dIE_6}{dt} = ageIE_5 + (1-\xi)a_6 CE_6 - (\rho + age + \mu_{6,t})IE_6$$
$$\frac{dRE_6}{dt} = ageRE_5 + \rho IE_6 + \alpha CE_6 - (\phi + w_S + age + \mu_{6,t})RE_6$$

Last age group

$$\frac{dS_{100}}{dt} = ageS_{99} + \phi R_{100} - \theta\lambda_{100}S_{100} - \mu_{100,t}S_{100} + w_L SV_{100} + w_S SE_{100}$$
$$\frac{dC_{100}}{dt} = ageC_{99} + \theta\lambda_{100}S_{100} + (a_{100} - \alpha - \mu_{100,t})C_{100} + w_L CV_{100} + w_S CE_{100}$$
$$\frac{dI_{100}}{dt} = ageI_{99} + a_{100}C_{100} - (\rho + \mu_{100,t})I_{100}$$
$$\frac{dR_{100}}{dt} = ageR_{99} + \rho I_{100} + \alpha C_{100} - (\phi + \mu_{100,t})R_{100} + w_L RV_{100} + w_S RE_{100}$$
$$\frac{dSV_{100}}{dt} = ageSV_{99} - (1-\delta)\theta\lambda_{100}SV_{100} + \phi RV_{100} - (w_L + \mu_{100,t})SV_{100}$$
$$\frac{dCV_{100}}{dt} = ageCV_{99} + (1-\delta)\theta\lambda_{100}SV_{100} - ((1-\xi)a_{100} + \alpha + w_L + \mu_{100,t})CV_{100}$$
$$\frac{dIV_{100}}{dt} = ageIV_{99} + (1-\xi)a_{100}CV_{100} - (\rho + \mu_{100,t})IV_{100}$$
$$\frac{dRV_{100}}{dt} = ageRV_{99} + \rho IV_{100} + \alpha CV_{100} - (\phi + w_L + \mu_{100,t})RV_{100}$$
$$\frac{dSE_{100}}{dt} = ageSE_{99} - (1-\delta)\theta\lambda_{100}SE_{100} + \phi RE_{100} - (w_S + \mu_{100,t})SE_{100}$$
$$\frac{dCE_{100}}{dt} = ageCE_{99} + (1-\delta)\theta\lambda_{100}SE_{100} - ((1-\xi)a_{100} + \alpha + w_S + \mu_{100,t})CE_{100}$$
$$\frac{dIE_{100}}{dt} = ageIE_{99} + (1-\xi)a_{100}CE_{100} - (\rho + \mu_{100,t})IE_{100}$$
$$\frac{dRE_{100}}{dt} = ageRE_{99} + \rho IE_{100} + \alpha CE_{100} - (\phi + w_S + \mu_{100,t})RE_{100}$$

Set of differential equations describing EPI at 10 years

Fist age group

$$\frac{dS_1}{dt} = B_t N + \phi R_1 - \theta\lambda_1 S_1 - (age + \mu_{1,t})S_1 + w_L SV_1 + w_S SE_1$$
$$\frac{dC_1}{dt} = \theta\lambda_1 S_1 + (a_1 - \alpha - \mu_{1,t} - age)C_1 + w_L CV_1 + w_S CE_1$$
$$\frac{dI_1}{dt} = a_1 C_1 - (\rho + age + \mu_{1,t})I_1$$
$$\frac{dR_1}{dt} = \rho I_1 + \alpha C_1 - (\phi + age + \mu_{1,t})R_1 + w_L RV_1 + w_S RE_1$$
$$\frac{dSV_1}{dt} = -(1-\delta)\theta\lambda_1 SV_1 + \phi RV_1 - (w_L + age + \mu_{1,t})SV_1$$
$$\frac{dCV_1}{dt} = (1-\delta)\theta\lambda_1 SV_1 - ((1-\xi)a_1 + \alpha + w_L + age + \mu_{1,t})CV_1$$
$$\frac{dIV_1}{dt} = (1-\xi)a_1 CV_1 - (\rho + age + \mu_{1,t})IV_1$$
$$\frac{dRV_1}{dt} = \rho IV_1 + \alpha CV_1 - (\phi + w_L + age + \mu_{1,t})RV_1$$
$$\frac{dSE_1}{dt} = -(1-\delta)\theta\lambda_1 SE_1 + \phi RE_1 - (w_S + age + \mu_{1,t})SE_1$$
$$\frac{dCE_1}{dt} = (1-\delta)\theta\lambda_1 SE_1 - ((1-\xi)a_1 + \alpha + w_S + age + \mu_{1,t})CE_1$$
$$\frac{dIE_1}{dt} = (1-\xi)a_1 CE_1 - (\rho + age + \mu_{1,t})IE_1$$
$$\frac{dRE_1}{dt} = \rho IE_1 + \alpha CE_1 - (\phi + w_S + age + \mu_{1,t})RE_1$$

Age groups $i = 2, ..., 10$ & age groups $i = 12, ..., 99$

$$\frac{dS_i}{dt} = ageS_{i-1} + \phi R_i - \theta\lambda_i S_i - (age + \mu_{i,t})S_i + w_L SV_i + w_S SE_i$$
$$\frac{dC_i}{dt} = ageC_{i-1} + \theta\lambda_i S_i + (a_i - \alpha - \mu_{i,t} - age)C_i + w_L CV_i + w_S CE_i$$
$$\frac{dI_i}{dt} = ageI_{i-1} + a_i C_i - (\rho + age + \mu_{i,t})I_i$$
$$\frac{dR_i}{dt} = ageR_{i-1} + \rho I_i + \alpha C_i - (\phi + age + \mu_{i,t})R_i + w_L RV_i + w_S RE_i$$
$$\frac{dSV_i}{dt} = ageSV_{i-1} - (1-\delta)\theta\lambda_i SV_i + \phi RV_i - (w_L + age + \mu_{i,t})SV_i$$
$$\frac{dCV_i}{dt} = ageCV_{i-1} + (1-\delta)\theta\lambda_i SV_i - ((1-\xi)a_i + \alpha + w_L + age + \mu_{i,t})CV_i$$

$$\frac{dIV_i}{dt} = ageIV_{i-1} + (1-\xi)a_iCV_i - (\rho + age + \mu_{i,t})IV_i$$
$$\frac{dRV_i}{dt} = ageRV_{i-1} + \rho IV_i + \alpha CV_i - (\phi + w_L + age + \mu_{i,t})RV_i$$
$$\frac{dSE_i}{dt} = ageSE_{i-1} - (1-\delta)\theta\lambda_i SE_i + \phi RE_i - (w_S + age + \mu_{i,t})SE_i$$
$$\frac{dCE_i}{dt} = ageCE_{i-1} + (1-\delta)\theta\lambda_i SE_i - ((1-\xi)a_i + \alpha + w_S + age + \mu_{i,t})CE_i$$
$$\frac{dIE_i}{dt} = ageIE_{i-1} + (1-\xi)a_iCE_i - (\rho + age + \mu_{i,t})IE_i$$
$$\frac{dRE_i}{dt} = ageRE_{i-1} + \rho IE_i + \alpha CE_i - (\phi + w_S + age + \mu_{i,t})RE_i$$

Age group 11

$$\frac{dS_{11}}{dt} = (1-\gamma_t)ageS_{10} + \phi R_{11} - \theta\lambda_{11}S_{11} - (age + \mu_{11,t})S_{11} + w_L SV_{11} + w_S SE_{11}$$
$$\frac{dC_{11}}{dt} = (1-\gamma_t)ageC_{10} + \theta\lambda_{11}S_{11} + (a_{11} - \alpha - \mu_{11,t} - age)C_{11} + w_L CV_{11} + w_S CE_{11}$$
$$\frac{dI_{11}}{dt} = ageI_{10} + a_{11}C_{11} - (\rho + age + \mu_{11,t})I_{11}$$
$$\frac{dR_{11}}{dt} = (1-\gamma_t)ageR_{10} + \rho I_{11} + \alpha C_{11} - (\phi + age + \mu_{11,t})R_{11} + w_L RV_{11} + w_S RE_{11}$$
$$\frac{dSV_{11}}{dt} = ageSV_{10} - (1-\delta)\theta\lambda_{11}SV_{11} + \phi RV_{11} - (w_L + age + \mu_{11,t})SV_{11} + \gamma_t ageS_{10}$$
$$\frac{dCV_{11}}{dt} = ageCV_{10} + (1-\delta)\theta\lambda_{11}SV_{11} - ((1-\xi)a_{11} + \alpha + w_L + age + \mu_{11,t})CV_{11} + \gamma_t C_{10}$$
$$\frac{dIV_{11}}{dt} = ageIV_{10} + (1-\xi)a_{11}CV_{11} - (\rho + age + \mu_{11,t})IV_{11}$$
$$\frac{dRV_{11}}{dt} = ageRV_{10} + \rho IV_{11} + \alpha CV_{11} - (\phi + w_L + age + \mu_{11,t})RV_{11} + \gamma_t R_{10}$$
$$\frac{dSE_{11}}{dt} = ageSE_{10} - (1-\delta)\theta\lambda_{11}SE_{11} + \phi RE_{11} - (w_S + age + \mu_{11,t})SE_{11}$$
$$\frac{dCE_{11}}{dt} = ageCE_{10} + (1-\delta)\theta\lambda_{11}SE_{11} - ((1-\xi)a_{11} + \alpha + w_S + age + \mu_{11,t})CE_{11}$$
$$\frac{dIE_{11}}{dt} = ageIE_{10} + (1-\xi)a_{11}CE_{11} - (\rho + age + \mu_{11,t})IE_{11}$$
$$\frac{dRE_{11}}{dt} = ageRE_{10} + \rho IE_{11} + \alpha CE_{11} - (\phi + w_S + age + \mu_{11,t})RE_{11}$$

Last age group

$$\frac{dS_{100}}{dt} = ageS_{99} + \phi R_{100} - \theta\lambda_{100}S_{100} - \mu_{100,t}S_{100} + w_L SV_{100} + w_S SE_{100}$$
$$\frac{dC_{100}}{dt} = ageC_{99} + \theta\lambda_{100}S_{100} + (a_{100} - \alpha - \mu_{100,t})C_{100} + w_L CV_{100} + w_S CE_{100}$$
$$\frac{dI_{100}}{dt} = ageI_{99} + a_{100}C_{100} - (\rho + \mu_{100,t})I_{100}$$
$$\frac{dR_{100}}{dt} = ageR_{99} + \rho I_{100} + \alpha C_{100} - (\phi + \mu_{100,t})R_{100} + w_L RV_{100} + w_S RE_{100}$$
$$\frac{dSV_{100}}{dt} = ageSV_{99} - (1-\delta)\theta\lambda_{100}SV_{100} + \phi RV_{100} - (w_L + \mu_{100,t})SV_{100}$$
$$\frac{dCV_{100}}{dt} = ageCV_{99} + (1-\delta)\theta\lambda_{100}SV_{100} - ((1-\xi)a_{100} + \alpha + w_L + \mu_{100,t})CV_{100}$$
$$\frac{dIV_{100}}{dt} = ageIV_{99} + (1-\xi)a_{100}CV_{100} - (\rho + \mu_{100,t})IV_{100}$$
$$\frac{dRV_{100}}{dt} = ageRV_{99} + \rho IV_{100} + \alpha CV_{100} - (\phi + w_L + \mu_{100,t})RV_{100}$$
$$\frac{dSE_{100}}{dt} = ageSE_{99} - (1-\delta)\theta\lambda_{100}SE_{100} + \phi RE_{100} - (w_S + \mu_{100,t})SE_{100}$$
$$\frac{dCE_{100}}{dt} = ageCE_{99} + (1-\delta)\theta\lambda_{100}SE_{100} - ((1-\xi)a_{100} + \alpha + w_S + \mu_{100,t})CE_{100}$$
$$\frac{dIE_{100}}{dt} = ageIE_{99} + (1-\xi)a_{100}CE_{100} - (\rho + \mu_{100,t})IE_{100}$$
$$\frac{dRE_{100}}{dt} = ageRE_{99} + \rho IE_{100} + \alpha CE_{100} - (\phi + w_S + \mu_{100,t})RE_{100}$$

Set of differential equations describing Booster at 5 years

Fist age group

$$\frac{dS_1}{dt} = B_t N + \phi R_1 - \theta\lambda_1 S_1 - (age + \mu_{1,t})S_1 + w_L SV_1 + w_S SE_1$$
$$\frac{dC_1}{dt} = \theta\lambda_1 S_1 + (a_1 - \alpha - \mu_{1,t} - age)C_1 + w_L CV_1 + w_S CE_1$$
$$\frac{dI_1}{dt} = a_1 C_1 - (\rho + age + \mu_{1,t})I_1$$
$$\frac{dR_1}{dt} = \rho I_1 + \alpha C_1 - (\phi + age + \mu_{1,t})R_1 + w_L RV_1 + w_S RE_1$$
$$\frac{dSV_1}{dt} = -(1-\delta)\theta\lambda_1 SV_1 + \phi RV_1 - (w_L + age + \mu_{1,t})SV_1$$
$$\frac{dCV_1}{dt} = (1-\delta)\theta\lambda_1 SV_1 - ((1-\xi)a_1 + \alpha + w_L + age + \mu_{1,t})CV_1$$
$$\frac{dIV_1}{dt} = (1-\xi)a_1 CV_1 - (\rho + age + \mu_{1,t})IV_1$$
$$\frac{dRV_1}{dt} = \rho IV_1 + \alpha CV_1 - (\phi + w_L + age + \mu_{1,t})RV_1$$
$$\frac{dSE_1}{dt} = -(1-\delta)\theta\lambda_1 SE_1 + \phi RE_1 - (w_S + age + \mu_{1,t})SE_1$$
$$\frac{dCE_1}{dt} = (1-\delta)\theta\lambda_1 SE_1 - ((1-\xi)a_1 + \alpha + w_S + age + \mu_{1,t})CE_1$$
$$\frac{dIE_1}{dt} = (1-\xi)a_1 CE_1 - (\rho + age + \mu_{1,t})IE_1$$
$$\frac{dRE_1}{dt} = \rho IE_1 + \alpha CE_1 - (\phi + w_S + age + \mu_{1,t})RE_1$$

Second age group

$$\frac{dS_2}{dt} = (1-\gamma_{1,t})ageS_1 + \phi R_2 - \theta\lambda_2 S_2 - (age + \mu_{2,t})S_2 + w_L SV_2 + w_S SE_2$$
$$\frac{dC_2}{dt} = (1-\gamma_{1,t})ageC_1 + \theta\lambda_2 S_2 + (a_2 - \alpha - \mu_{2,t} - age)C_2 + w_L CV_2 + w_S CE_2$$
$$\frac{dI_2}{dt} = ageI_1 + a_2 C_2 - (\rho + age + \mu_{2,t})I_2$$
$$\frac{dR_2}{dt} = (1-\gamma_{1,t})ageR_1 + \rho I_2 + \alpha C_2 - (\phi + age + \mu_{2,t})R_2 + w_L RV_2 + w_S RE_2$$
$$\frac{dSV_2}{dt} = ageSV_1 - (1-\delta)\theta\lambda_2 SV_2 + \phi RV_2 - (w_L + age + \mu_{2,t})SV_2$$
$$\frac{dCV_2}{dt} = ageCV_1 + (1-\delta)\theta\lambda_2 SV_2 - ((1-\xi)a_2 + \alpha + w_L + age + \mu_{2,t})CV_2$$

$$\frac{dIV_2}{dt} = ageIV_1 + (1-\xi)a_2CV_2 - (\rho + age + \mu_{2,t})IV_2$$
$$\frac{dRV_2}{dt} = ageRV_1 + \rho IV_2 + \alpha CV_2 - (\phi + w_L + age + \mu_{2,t})RV_2$$
$$\frac{dSE_2}{dt} = ageSE_1 - (1-\delta)\theta\lambda_2 SE_2 + \phi RE_2 - (w_S + age + \mu_{2,t})SE_2 + \gamma_{1,t}ageS_1$$
$$\frac{dCE_2}{dt} = ageCE_1 + (1-\delta)\theta\lambda_2 SE_2 - ((1-\xi)a_2 + \alpha + w_S + age + \mu_{2,t})CE_2 + \gamma_{1,t}C_1$$
$$\frac{dIE_2}{dt} = ageIE_1 + (1-\xi)a_2CE_2 - (\rho + age + \mu_{2,t})IE_2$$
$$\frac{dRE_2}{dt} = ageRE_1 + \rho IE_2 + \alpha CE_2 - (\phi + w_S + age + \mu_{2,t})RE_2 + \gamma_{1,t}R_1$$

Age groups $i = 3, ..., 5$ & age groups $i = 7, ..., 99$

$$\frac{dS_i}{dt} = ageS_{i-1} + \phi R_i - \theta\lambda_i S_i - (age + \mu_{i,t})S_i + w_L SV_i + w_S SE_i$$
$$\frac{dC_i}{dt} = ageC_{i-1} + \theta\lambda_i S_i + (a_i - \alpha - \mu_{i,t} - age)C_i + w_L CV_i + w_S CE_i$$
$$\frac{dI_i}{dt} = ageI_{i-1} + a_i C_i - (\rho + age + \mu_{i,t})I_i$$
$$\frac{dR_i}{dt} = ageR_{i-1} + \rho I_i + \alpha C_i - (\phi + age + \mu_{i,t})R_i + w_L RV_i + w_S RE_i$$
$$\frac{dSV_i}{dt} = ageSV_{i-1} - (1-\delta)\theta\lambda_i SV_i + \phi RV_i - (w_L + age + \mu_{i,t})SV_i$$
$$\frac{dCV_i}{dt} = ageCV_{i-1} + (1-\delta)\theta\lambda_i SV_i - ((1-\xi)a_i + \alpha + w_L + age + \mu_{i,t})CV_i$$
$$\frac{dIV_i}{dt} = ageIV_{i-1} + (1-\xi)a_i CV_i - (\rho + age + \mu_{i,t})IV_i$$
$$\frac{dRV_i}{dt} = ageRV_{i-1} + \rho IV_i + \alpha CV_i - (\phi + w_L + age + \mu_{i,t})RV_i$$
$$\frac{dSE_i}{dt} = ageSE_{i-1} - (1-\delta)\theta\lambda_i SE_i + \phi RE_i - (w_S + age + \mu_{i,t})SE_i$$
$$\frac{dCE_i}{dt} = ageCE_{i-1} + (1-\delta)\theta\lambda_i SE_i - ((1-\xi)a_i + \alpha + w_S + age + \mu_{i,t})CE_i$$
$$\frac{dIE_i}{dt} = ageIE_{i-1} + (1-\xi)a_i CE_i - (\rho + age + \mu_{i,t})IE_i$$
$$\frac{dRE_i}{dt} = ageRE_{i-1} + \rho IE_i + \alpha CE_i - (\phi + w_S + age + \mu_{i,t})RE_i$$

Age group 6

$$\frac{dS_6}{dt} = (1-\gamma_{2,t})ageS_5 + \phi R_6 - \theta\lambda_6 S_6 - (age+\mu_{6,t})S_6 + w_L SV_6 + w_S SE_6$$
$$\frac{dC_6}{dt} = (1-\gamma_{2,t})ageC_5 + \theta\lambda_6 S_6 + (a_6 - \alpha - \mu_{6,t} - age)C_6 + w_L CV_6 + w_S CE_6$$
$$\frac{dI_6}{dt} = ageI_5 + a_6 C_6 - (\rho + age + \mu_{6,t})I_6$$
$$\frac{dR_6}{dt} = (1-\gamma_{2,t})ageR_5 + \rho I_6 + \alpha C_6 - (\phi + age + \mu_{6,t})R_6 + w_L RV_6 + w_S RE_6$$
$$\frac{dSV_6}{dt} = ageSV_5 - (1-\delta)\theta\lambda_6 SV_6 + \phi RV_6 - (w_L + age + \mu_{6,t})SV_6 + \gamma_{2,t}ageS_5 + \gamma_{2,t}ageSE_5$$
$$\frac{dCV_6}{dt} = ageCV_5 + (1-\delta)\theta\lambda_6 SV_6 - ((1-\xi)a_6 + \alpha + w_L + age + \mu_{6,t})CV_6 + \gamma_{2,t}C_5 + \gamma_{2,t}CE_5$$
$$\frac{dIV_6}{dt} = ageIV_5 + (1-\xi)a_6 CV_6 - (\rho + age + \mu_{6,t})IV_6$$
$$\frac{dRV_6}{dt} = ageRV_5 + \rho IV_6 + \alpha CV_6 - (\phi + w_L + age + \mu_{6,t})RV_6 + \gamma_{2,t}R_5 + \gamma_{2,t}RE_5$$
$$\frac{dSE_6}{dt} = (1-\gamma_{6,t})ageSE_5 - (1-\delta)\theta\lambda_6 SE_6 + \phi RE_6 - (w_S + age + \mu_{6,t})SE_6$$
$$\frac{dCE_6}{dt} = (1-\gamma_{2,t})ageCE_5 + (1-\delta)\theta\lambda_6 SE_6 - ((1-\xi)a_6 + \alpha + w_S + age + \mu_{2,t})CE_6 + \gamma_{1,t}C_6$$
$$\frac{dIE_6}{dt} = ageIE_5 + (1-\xi)a_6 CE_6 - (\rho + age + \mu_{6,t})IE_6$$
$$\frac{dRE_6}{dt} = (1-\gamma_{2,t})ageRE_5 + \rho IE_6 + \alpha CE_6 - (\phi + w_S + age + \mu_{6,t})RE_6$$

Last age group

$$\frac{dS_{100}}{dt} = ageS_{99} + \phi R_{100} - \theta\lambda_{100} S_{100} - \mu_{100,t}S_{100} + w_L SV_{100} + w_S SE_{100}$$
$$\frac{dC_{100}}{dt} = ageC_{99} + \theta\lambda_{100} S_{100} + (a_{100} - \alpha - \mu_{100,t})C_{100} + w_L CV_{100} + w_S CE_{100}$$
$$\frac{dI_{100}}{dt} = ageI_{99} + a_{100} C_{100} - (\rho + \mu_{100,t})I_{100}$$
$$\frac{dR_{100}}{dt} = ageR_{99} + \rho I_{100} + \alpha C_{100} - (\phi + \mu_{100,t})R_{100} + w_L RV_{100} + w_S RE_{100}$$
$$\frac{dSV_{100}}{dt} = ageSV_{99} - (1-\delta)\theta\lambda_{100} SV_{100} + \phi RV_{100} - (w_L + \mu_{100,t})SV_{100}$$

$$\frac{dCV_{100}}{dt} = ageCV_{99} + (1-\delta)\theta\lambda_{100}SV_{100} - ((1-\xi)a_{100} + \alpha + w_L + \mu_{100,t})CV_{100}$$
$$\frac{dIV_{100}}{dt} = ageIV_{99} + (1-\xi)a_{100}CV_{100} - (\rho + \mu_{100,t})IV_{100}$$
$$\frac{dRV_{100}}{dt} = ageRV_{99} + \rho IV_{100} + \alpha CV_{100} - (\phi + w_L + \mu_{100,t})RV_{100}$$
$$\frac{dSE_{100}}{dt} = ageSE_{99} - (1-\delta)\theta\lambda_{100}SE_{100} + \phi RE_{100} - (w_S + \mu_{100,t})SE_{100}$$
$$\frac{dCE_{100}}{dt} = ageCE_{99} + (1-\delta)\theta\lambda_{100}SE_{100} - ((1-\xi)a_{100} + \alpha + w_S + \mu_{100,t})CE_{100}$$
$$\frac{dIE_{100}}{dt} = ageIE_{99} + (1-\xi)a_{100}CE_{100} - (\rho + \mu_{100,t})IE_{100}$$
$$\frac{dRE_{100}}{dt} = ageRE_{99} + \rho IE_{100} + \alpha CE_{100} - (\phi + w_S + \mu_{100,t})RE_{100}$$